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THE TWO-SOLVENT METHOD

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In a study of the equilibria between liquid phases in ternary systems it was proved that their regions of separation reflect interaction between the components of the prevailing binary systems [1], that is, systems the interaction in which prevails over that in the other two binary systems. Various processes may occur in the prevailing binary system of a given ternary system, one of the most important of which is the formation of chemical compounds by the components. This process may be reflected by the region of separation of the ternary system in various geometrical forms: as a single edge [1], as a triple critical point [2], as a solubility maximum [3] or minimum in a closed isotherm [4]. Instances also occur when the formation of chemical compounds in the prevailing system is not reflected by any geometrical form in the region of separation of the ternary system [5], or is reflected in a distorted form, when these geometrical forms represent not the composition of the chemical compounds formed, but some other irrational composition [6].

The prevailing system and the chemical compounds formed in it must be considered only in an integrated relationship with the third component which acts as the solvent, and in a state of mutual dependence with it. The exceptionally powerful influence of various solvents on the nature of chemical processes has been demonstrated earlier [7]. Closely associated with this is the no less powerful influence of solvents on the properties of the compounds formed. Study of this problem, particularly in recent years [8], showed that the solvent can modify the properties and structure of compounds to a considerable extent. It was established that the solvent, by selective action, may favor or hinder the stabilization of individual molecular forms, and that intramolecular changes and intermolecular interaction are inextricably interrelated.

Thus, interaction in a binary prevailing system is inextricably bound with its relationships with the third component. The multiplicity of such relationships is the cause for the multiplicity of the forms in which chemical action in the prevailing system is reflected by the region of separation of the ternary system. Consequently, the geometrical form of the region of separation in a ternary system is the result of interaction both within the prevailing system and between it and the third component.

For these reasons a study of the interaction of the binary system in only one solvent in many instances cannot provide full information on the nature of the interaction between the components of the system and on the properties of the compounds formed, but sometimes a whole series of solvents may have effects of the same type on a binary reacting system. For example, the binary system acetic anhydride – water was studied in gasoline [1] and carbon disulfide [9]; surfaces of both ternary systems showed similar synclinal singular edges, which in all cases corresponded to the composition of acetic acid formed in the prevailing system.

Among the properties of a solvent, its polarity has a particularly powerful effect both on the nature of the interaction in the reacting binary system and on the properties of the compounds formed in it. It is therefore proposed to study the demixing of binary reacting systems in two solvents, polar and nonpolar, and to term this the two-solvent method.

Among the ternary systems in which demixing occurs, reported in the literature, there is only a single instance when a binary system, namely aniline – acetic acid, was studied with respect to its demixing behavior by different authors at different times in polar and nonpolar solvents. In the ternary system aniline – acetic acid – water [10], the chemical action between aniline and acetic acid is not reflected in any way on the demixing isotherm for the system. In the ternary system aniline – acetic acid – benzine, the compound $2C_6H_5NH_2 \cdot CH_3COOH$ is represented on the separation surface by a synclinal singular edge [11]. However, these systems only agree fortuitously with the aims described above, and the literature contains no special investigations of the problem.

EXPERIMENTAL

For confirmation of the above views, the demixing of the binary system antipyrine – salicyclic acid was studied in two solvents, one strongly polar – water (the dipole moment for water is $1.84 \cdot 10^{18}$ [12]), and one nonpolar – gaso-

line. Thus, the ternary system antipyrine – salicylic acid – water, and the conditionally ternary system antipyrine – salicylic acid – gasoline were investigated.

The following substances were used for the work: pharmaceutical antipyrine, m.p. 113°, salicylic acid, chemically pure grade, m.p. 155°, twice-distilled water, and a gasoline fraction boiling in the 120-140° range.

The binary systems which compose the ternary systems studied have the following properties. Antipyrine is a strong monoacid base, and therefore salt formation takes place in the binary system antipyrine – salicylic acid, with the formation of salipyrine, known for its medical applications. In fact, a study of the melting behavior of this system [13] showed the formation of a single chemical compound, with m.p. 89°, which contains 43.2% salicylic acid and 56.8% antipyrine, corresponding to a molecular ratio of 1:1 between salicylic acid and antipyrine. Antipyrine has unlimited solubility in water, while its solubility in benzine is limited (as shown in the present paper) by a very high critical solubility temperature. Salicylic acid has unlimited solubility in gasoline. The melting and demixing behavior of the binary system salicylic acid – water has been studied [14], and the system was shown to have an unstable equilibrium curve between the liquid phases with an upper critical point at 89.1°, but in the present work it served as a homogeneous system, as because of the high melting points of the components and of salipyrine it was necessary to conduct the study at temperatures above the given critical value. In both ternary systems studied, the binary system antipyrine – salicylic acid is the prevailing system.

The experiments were performed by the usual polythermic method [15] in sealed glass ampoules in an oil thermostat. The three-component systems were studied by polythermic sections through their prisms, taken from the edge for water (or gasoline) to the plane for the binary system antipyrine – salicylic acid.

The ternary system antipyrine – salicylic acid – water. 9 polythermic sections were studied, corresponding to 20, 30, 43, 50, 60, 70, 80, 90 and 95%• of salicylic acid. The numerical results for the sections are shown in Table 1 and Fig. 1. As Figure 1 shows, all the polytherms have a qualitatively similar appearance with solubility maxima, which increase from sections 1 to 4, and decrease from sections 4 to 9. In most of the polytherms the maxima are shifted toward the edge for water. In all the sections (Table 1) the solubility of water in antipyrine – salicylic acid mixtures is approximately double the solubility of these mixtures in water. At the edges of the polytherms the mutual solubility in the system is affected little by the temperature, and the curves ascend steeply. As the temperatures of mixing are approached, however, the temperature has a strong effect, and therefore the maxima on the polytherms are very flat.

The polytherms were used to construct 6 solubility isotherms for the given ternary system at 100, 110, 140, 145, 150 and 160°, shown in Fig. 4, where the point S corresponds to the composition of salipyrine. As Fig. 4 shows, all the isotherms are closed curves which diminish concentrically with rise of temperature. Thus, the three-component system studied has an upper triple critical point at 170° which corresponds to the composition: 18% antipyrine, 22% salicylic acid, and 60% water. All the isotherms have minima for the mutual solubility of water and antipyrine – salicylic acid mixtures. At relatively low temperatures, of the order of 100-110°, these solubility minima lie in the section which corresponds to the salipyrine composition in the binary system antipyrine – salicylic acid. As the temperature increases, they deviate somewhat from this section in the direction of the salicylic acid edge, as shown by the broken line in Fig. 4.

Such instances of a certain deviation of liquid phase solubility minima from the composition of the chemical compound have also been observed previously [16] in ternary systems in which demixing occurs. The cause of this is still insufficiently studied. In such instances it was merely assumed that, as the temperature rises, there is increased interaction between the compound formed in the prevailing binary system (in this instance salipyrine) and the component in the direction of which the deviation occurs (in this instance salicylic acid). It is likely that this effect is closely associated with increased interaction between antipyrine and water with rise of temperature, and is thus the consequence of the influence of the solvent on the equilibrium in the reacting system, and partial decomposition of salipyrine at higher temperatures is also possible here.

Although the given ternary system was studied in the region of stable equilibrium between the liquid phases, it nevertheless contains the binary system salicylic acid – water with unstable demixing properties. Thus it is a ternary system type with a transition from an unstable to a stable liquid phase equilibrium, namely, a type in which this unstable binary equilibrium is homogenized in the ternary system on passage through the upper critical triple point for stable equilibrium. In the present instance the homogenization is effected by antipyrine.

• The percentages are by weight in all instances.

TABLE 1

Polytherms for the System Antipyrine – Salicylic Acid – Water

Section No.	Water (% by weight)	Demixing temperature	Section No.	Water (% by weight)	Demixing temperature	Section No.	Water (% by weight)	Demixing temper	Section No.	Water (% by weight)	Demixing temperature
							8.80	98.0°			
							11.30	111.5		10.50	108.0°
	40.00	98.0°		10.00	52.0°		15.86	125.0		20.63	145.0
1	50.00	113.0	2	20.64	99.0	3	23.35	145.0	4	30.59	160.0
20%	60.00	125.0	30%	30.00	130.0	43%	32.00	156.0	50%	40.00	167.0
S.A.*	70.00	133.0	S.A.	55.00	148.0	S.A.	47.40	162.0	S.A	65.00	166.0
80%	80.00	128.0	70%	80.00	146.0	57%	65.07	163.0	50%	78.00	161.0
A.*	90.00	118.0	A.	90.10	131.0	A.	80.00	156.0	A.	90.00	143.0
				95.02	106.0		90.98	136.0		95.00	118.0
							94.97	115.0			
	10.13	100.0		10.00	79.0		97.10	90.0			
	15.03	127.5		20.00	128.5		21.02	107.0		30.00	94.0
5	21.08	145.0	6	30.00	149.0	7	30.07	131.0	8	35.00	107.0
60%	40.00	164.0	70%	40.00	156.0	80%	40.00	144.0	90%	45.27	115.0
S.A.	60.00	166.0	S.A.	50.00	159.0	S.A.	52.10	145.0	S.A.	50.19	119.0
40%	75.00	160.0	30%	60.00	161.0	20%	60.40	146.0	10%	60.63	124.0
A.	90.05	143.0	A.	70.00	160.0	A.	70.70	149.5	A.	69.90	129.0
	95.00	119.0		80.00	154.0		80.20	148.0		80.00	132.0
				90.00	140.0		90.09	134.0		90.00	120.0
				95.00	114.0					98.70	108.0
	40.00	96.0									
9	50.00	104.0									
95%	60.00	108.0									
S.A.	70.00	110.0									
5% A	80.39	116.0									
	90.00	111.0									

* S. A. is salicylic acid, A is antipyrine.

The conditionally binary system antipyrine – gasoline was studied with respect to its demixing behavior in order to obtain data for investigation of the ternary system antipyrine – salicylic acid – gasoline. The numerical data obtained are shown in Table 2, and the solubility curves are shown in Fig. 2. It is seen from Fig. 2, that the mutual solubility of the components at low temperatures is not high, of the order of 5-10%, but it increases with rise of temperature, and therefore an upper critical point should exist here also. However, it was not reached because of the high temperatures at which it is to be found.

It should be pointed out that though gasoline is not an individual substance, but a mixture, it has been extensively used in work on equilibrium liquid systems. The reason is that gasoline is a mixture of substances of similar physico-chemical behavior, nonpolar hydrocarbons, and therefore its use instead of the individual hydrocarbons could only affect the diagram quantitatively and not qualitatively. However, the use of gasoline as a nonpolar solvent has the positive aspect that it results in the generalization of the behavior of a whole class of compounds, the hydrocarbons.

The ternary system antipyrine – salicylic acid – gasoline. 8 polythermic sections were studied for this system, with salicylic acid contents of 15, 30, 43, 50, 60, 70, 80 and 90%. The numerical data are presented in Table 3, and the solubility polytherms are shown in Fig. 3. The polytherms for the ternary systems are qualitatively similar to the equilibrium curves between the liquid phases in the binary system antipyrine – gasoline, and for the same reason, namely that in most of them the maximum temperatures of mixing were not reached. The polytherms show that the

solubility of gasoline in antipyrine – salicylic acid mixtures is much higher than the solubility of these mixtures in gasoline. In this temary system the effect of temperature on the solubility is not great, and therefore the polytherms ascend steeply.

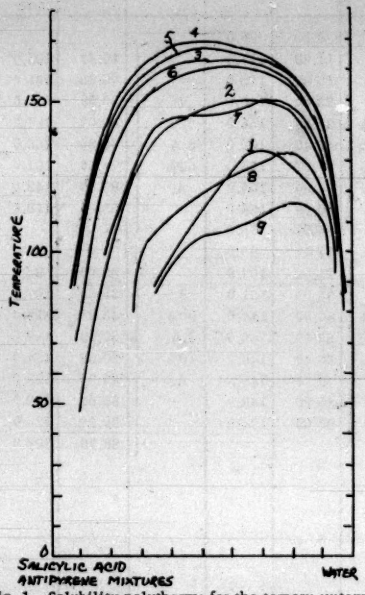

Fig. 1. Solubility polytherms for the ternary system antipyrine – salicylic acid – water. Salicylic acid content (% by weight): 1-20, 2-30, 3-43, 4-50, 5-60, 6-70, 7-80, 8-90, 9-95.

The polytherms obtained were used to construct 4 solubility isotherms for the ternary system at 100, 140, 150 and 160°, which are shown in Fig. 5. The isotherms show that demixing of the binary system antipyrine – gasoline is homogenized by salicylic acid in the three-component system. The equilibrium surface between the liquid phases in the ternary system has a mutual solubility maximum for salipyrine and gasoline, which is singular in nature. The synclinal singular edge in the binary system antipyrine – salicylic acid is represented by the salipyrine composition, corresponding to the point S.

Thus, a section of the prism for the given ternary system along the singular edge, that is, a quasibinary section, divides it into two ternary systems. One of these, salipyrine – antipyrine – gasoline, is a ternary system with a demixing volume which joins the planes for the solubility breaks of its two binary systems, consisting of gasoline with antipyrine, and gasoline with salipyrine. In the other ternary system, salipyrine – salicylic acid – gasoline, demixing of the binary system salipyrine – gasoline is homogenized by salicylic acid. In both ternary systems the prevailing systems are homogeneous binary systems which do not contain gasoline.

A comparison of the demixing isotherms for the two above ternary systems shows that solvents with different polarities qualitatively modify the nature of the solubility of the binary system antipyrine – salicylic acid. It is therefore not a question of an increase or decrease of the solubility of salipyrine in this or that solvent, but of a qualitative change in the interaction between salipyrine and the solvent when the polar medium is replaced by a nonpolar.

TABLE 2

Liquid Phase Equilibrium in the System Antipyrine – Gasoline

Contents (% by weight)		Demixing temperature
gasoline	antipyrine	
10.25	89.75	110.0°
12.81	87.19	122.0
18.55	81.45	145.0
85.53	14.47	143.0
91.66	8.34	119.0
94.88	5.12	99.0
97.02	2.98	80.0

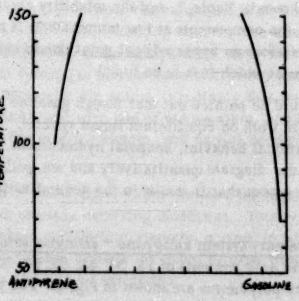

Fig. 2. Liquid phase equilibrium in the system antipyrine – gasoline

TABLE 3

Polytherms for the System Antipyrine – Salicylic Acid – Gasoline

Section No.	Gasoline (% by weight)	Demixing temperature	Section No.	Gasoline (% by weight)	Demixing temperature	Section No.	Gasoline (% by weight)	Demixing temperature	Section No.	Gasoline (% by weight)	Demixing temperature
	7.00	86.0°		7.50	84.0°		6.50	76.0°		7.50	84.0°
	10.90	117.0		10.00	111.0		8.90	100.0		10.00	102.0
1	12.00	128.0	2	15.00	145.0	3	10.00	111.0	4	13.20	138.0
15%	19.00	164.0	30%	18.00	161.0	43%	15.00	139.0	50%	19.00	163.0
S.A.*	86.00	162.5	S.A.	88.00	159.0	S.A.	20.00	160.0	S.A.	90.00	155.0
85%	90.00	149.0	70%	92.00	134.0	57%	90.00	159.0	50%	95.00	117.0
A.*	95.00	114.0	A.	95.00	120.0	A.	95.00	125.0	A.	96.00	114.0
	97.00	96.0		97.00	99 0		97.00	94.0		97.00	98.0
							21.00	99.0			
							22.00	109.0			
				13.00	95.0		25.00	122.0			
	8.00	85.0		15.00	120.0		30.00	139.0		45.00	95.0
5	10.00	100.0	6	20.00	145.0	7	35.00	149.0	8	50.00	110.0
60%	11.30	110.0	70%	23.00	154.0	80%	48.60	151.5	90%	60.00	123.0
S.A.	15.00	135.0	S.A.	27.00	162.0	S.A.	55.00	154.0	S.A.	70.00	128.0
40%	20.00	160.0	30%	80 00	178.0	20%	65.00	163.0	10%	80.00	132.0
A.	90.00	156.0	A.	90.00	154.0	A.	75.00	163.0	A.	85.00	125.0
	95.00	121.0		95.00	120.0		80.00	152.0		90.00	103.0
	97.00	96.0		97.00	98.0		85.00	139.0			
							90.00	123.0			
							94.00	109.0			

* S. A. is salicylic acid, A. is antipyrine.

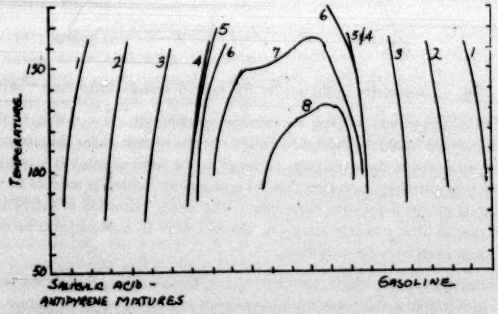

Fig. 3. Solubility polytherms for the ternary system antipyrine – salicylic acid – gasoline. Salicylic acid content (% by weight): 1-15, 2-30, 3-43, 4-50, 5-60, 6-70, 7-80, 8-90.

The ternary system antipyrine – salicylic acid – water consists, on the one hand, of components capable of strong hydration; antipyrine contains tertiary amino groups, while salicylic acid contains acid and phenolic groups. In addition, the acid is strongly polar (the dipole moment is $2.63 \cdot 10^{18}$ [12]). On the other hand, the system contains a strongly polar solvent, water; therefore solvation (specifically hydration) processes are predominantly developed in this ternary system; these processes strongly affect the interaction in the prevailing binary system and

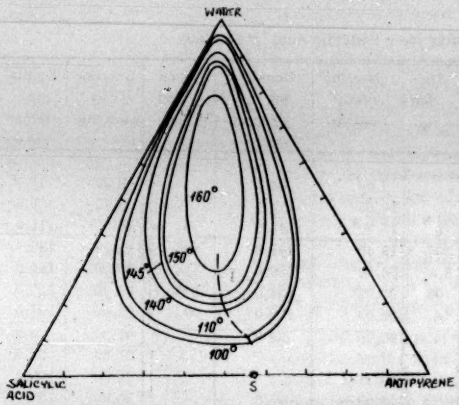

Fig. 4. Solubility isotherms for the ternary system antipyrine – salicylic acid – water.

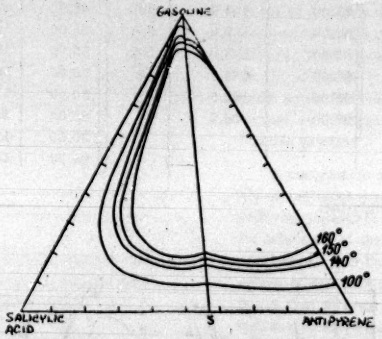

Fig. 5. Solubility isotherms for the ternary system antipyrine – salicylic acid – gasoline.

determine the relationships of the latter to the third component. In view of this, in the present instance salipyrine should be stabilized by the hydration processes. In the system under discussion, the formation of a solvation compound was reflected in the demixing isotherms in the form of solubility minima. This depends on the fact that salipyrine is less strongly hydrated than its components, which is natural in the prevailing system when some of the functional groups react with each other. The strong hydration of salicylic acid and antipyrine is confirmed (in addition to what was said above) by the fact that, in the temperature conditions studied, their solubility in water can even become unlimited.

In the other ternary system, where the properties of the chemical compound and of the components in the prevailing system in relation to the polar third component are of the opposite nature, a solubility maximum might have been obtained on the demixing isotherms if the chemical compound was still solvational in character. This did, in fact, occur in studies of unstable equilibria [17] in the ternary system picric acid – salicylic acid – water.

In the ternary system antipyrine – salicylic acid – gasoline, the latter is a nonpolar solvent; therefore

other processes predominate here, namely, the association of molecules and dissociation of associated molecules; these processes are strongly developed both in the prevailing system and in its relationships with the third component. In a nonpolar medium salipyrine may be stabilized not by hydration processes, but with the aid of association processes. In the present instance the formation of an association compound was reflected in the separation surface of the ternary system by a qualitatively different geometrical element, namely a synclinal singular edge. The formation of a singular solubility maximum in the conditions in question is, on the one hand, caused by the fact that salipyrine is in this instance associated into a stable complex, with a low tendency to dissociation in the ternary system mixtures, like the solvent molecules. On the other hand, it is caused by the fact that the components of the prevailing binary system show specific behavior toward salipyrine in the ternary system conditions. Indeed, as the isotherms for the given ternary system show, the relationship between antipyrine and salipyrine is almost normal; both have a low tendency to association in their mixtures in ternary system conditions, and the mutual solubility of their mixtures with gasoline changes little with change in the composition of the mixtures. By contrast, salicylic acid in mixtures with salipyrine is strongly dissociated in a nonpolar medium, and its mutual solubility with gasoline even becomes unlimited.

In another ternary system, with other relationships in the prevailing system and between the latter and the third component in a nonpolar medium, it might also be possible to find a solubility minimum on the demixing isotherms while the chemical compound in the prevailing system was still of an associational nature. This does, in fact, occur in the ternary systems allyl mustard oil – o-toluidine – sulfur, and allyl mustard oil – methylaniline – sulfur [18].

Consequently, the form of separation surface of a ternary system is determined not only by the compound formed in the prevailing system, and not only by the interaction of this compound with the solvent, but also by interaction both in the prevailing system as a whole, and between the latter and the third component. This confirms the view that demixing studies of a reacting system in one solvent type cannot give complete information on it.

The present study deals with an effect which is close to one of the types of molecular polymorphism [19], namely, the type in which, when the medium is changed from polar to nonpolar, there is a change in the form in which the chemical compound in solution becomes stabilized by conversion from a solvational to an associated state [20]. In the present instance there is a change in the qualitative character of the solubility of salipyrine in solvents with different polarities, which is reflected in the demixing isotherms by qualitatively different geometrical elements; in other words, salipyrine reacts differently with water and with gasoline, as solvents of different types. This also shows clearly that the two-solvent method for the investigation of demixing behavior of reacting systems makes it possible not only to determine the composition of the compounds formed, but also to determine the finest features and differences in their properties. By this method it is possible to detect details of chemical action to the extent of detection of all the chemical compounds formed in the prevailing system, when some of them (or all, as in the systems described in the literature) are not reflected in the separation surface of one of the ternary systems studied.

When a solvent in a ternary system is exchanged for another, some of the former relationships are replaced by others, and therefore the nature of the separation surface with respect to the same prevailing system is also changed. Topological transformations of the separation surface take place, and the ternary system is converted from one type into another. In the present investigation, a ternary system with an upper triple critical point was converted into a ternary system with a synclinal singular edge. By means of these transformations, which take place when the two-solvent method is used, it is possible to detect and clarify all the details of the chemical changes which occur in the reacting system.

It was found by experience that these two solvent types, polar and nonpolar, are quite sufficient for the solution of the principal problems in demixing investigations. In addition, it is even possible to indicate some general solvents for the study of most substances. For example, if the prevailing binary system consists of organic compounds, then in most cases water (or sometimes the higher alcohols) is convenient to use as the polar third component, while for the nonpolar component, saturated aliphatic hydrocarbons, carbon disulfide, or sulfur should be used (although the latter introduces certain complications by dissociation of its associated molecules and by reactions with organic compounds at high temperatures).

Certain conditions in the practical selection of the solvents must be fulfilled in the use of the two-solvent method for demixing studies on ternary systems. The polar and nonpolar solvents must be chosen for a given reacting binary system in such a manner that, on the one hand, one or both of its components would demix with the solvent or, if no demixing occurs between them, that it should occur between mixtures of the reacting system and the third

component with respect to it. On the other hand, the choice must be such that the binary system studied should always be the prevailing system in the ternary systems formed.

SUMMARY

1. A method is proposed for the study of equilibria between the liquid phases of ternary systems in two solvents, polar and nonpolar, and the theoretical basis for the method is discussed.

2. The two-solvent method was used to study the reaction between antipyrine and salicylic acid in the ternary systems: antipyrine – salicylic acid – water, and antipyrine – salicylic acid – gasoline. In the first of these, the salipyrine formed is shown in the separation surface as a solubility minimum with the formation of an upper triple critical point. In the second, salipyrine is shown as a solubility maximum in the form of a synclinal singular edge.

3. A comparison of the two equilibrium states shows that when the solvent is changed from polar to nonpolar, the interaction between salipyrine and the solvent changes also.

4. It is shown that by the use of the two-solvent method the conversion of ternary systems from one type to another is possible. A ternary system with an upper triple critical point was converted into a ternary system with a synclinal.

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THE RHENIUM – DIMETHYLGLYOXIME COMPLEX

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Rhenium compounds form an orange-red complex with dimethylglyoxime in aqueous and aqueous alcohol solutions [1]. Its composition is unknown. It was supposed that the valency of rhenium in this complex is three, since the reaction occurs in the presence of stannous chloride. The reaction was proposed for the qualitative detection of rhenium; its sensitivity is 1:100000 [2].

α-Benzyldioxime and α-furyldioxime also form colored complexes with rhenium in the presence of acids and stannous chloride. These complexes are used for the colorimetric determination of rhenium [3, 4]. It is stated in the literature that the valency of rhenium in its complex with α-benzyldioxime is greater than four and less than seven [3].

The reaction between rhenium and α-dioximes was studied more systematically by V. M. Peshkova and M. I. Gromova [5]. They studied the reactions between rhenium and methyl, dimethyl, and α-furyldioximes, and cyclohexanedione dioxime in the presence of sulfuric acid and stannous chloride. The complexes formed have different colors, but composition of the complexes was not studied. These authors supposed that the valency of rhenium in these complexes is four.

Thus, despite the importance of the use of rhenium – α-dioxime complexes in practice, their composition has not been studied.

The aim of the present work was the study of the composition of the rhenium – dimethylglyoxime complex in hydrochloric acid in the presence of stannous chloride.

The composition of the rhenium – dimethylglyoxime complex was studied by a physico-chemical method [6, 7] and by ion exchange chromatography. By studies of the light absorption of solutions it is possible to determine the composition of the colored complex without isolating it in the pure state. The method makes it possible to use low solution concentrations, which is very important for the study of the expensive and rare rhenium compounds.

By ion exchange chromatography the nature of the colored part of the complex may be easily established. If the colored part is absorbed when a solution of the complex is passed through a cationite, it is a cation. Anionites do not absorb such complexes. If the colored part of the complex is absorbed by an anionite, it is not absorbed by cationites, and is an anion.

EXPERIMENTAL

The light absorption of the solutions was studied with the aid of the FEK-2 photocolorimeter. The complex was prepared by consecutive mixing of the following solutions: 15 ml of hydrochloric acid (1:1), 2 ml of 1% dimethyl glyoxime in alcohol, 2 ml of 10% stannous chloride in hydrochloric acid (1:1), and the necessary amount of rhenium. The mixed solution was made up to 50 ml with distilled water and stirred. The color of the complex deepens with time and is stable a long time. The light absorption was measured after 20 minutes. The greatest absorption was found with the use of a light-blue light filter with transmission in 400-500 mμ. No light absorption maximum was found in the 400-750 mμ region of the spectrum studied, as it lies in the short wave region of the spectrum.

It proved impossible to extract the colored complex by any of many organic solvents: benzene, toluene, chloroform, dichloroethane, amyl and butyl alcohols, diethyl ether, ethyl acetate. This indicates the strongly hydrophilic character of the molecule of the complex.

The light absorption of rhenium – dimethylglyoxime complex solutions in the presence of acids and stannous chloride obeys the Lambert-Beer law over a wide range of concentrations (Fig. 1).

The solution system studied is represented by the triangular diagram rhenium – dimethylglyoxime (H_2Dm) – hydrochloric acid solution (Fig. 2).

The light absorption was studied along different sections of the diagram. The rhenium solution was prepared by dissolving potassium perrhenate, previously recrystallized from hot water, in dilute hydrochloric acid (1 : 20). Dimethylglyoxime, of "pure" grade, was twice recrystallized from alcohol. It was used in alcohol solution for the experiments. When the light absorption along the 1-2 Section was studied, the concentrations of the original solutions of potassium perrhenate and dimethylglyoxime were both $1.84 \cdot 10^{-3}$ molar. The sum of the volumes of the potassium perrhenate and dimethylglyoxime solutions was 10 ml, and the total concentration of the solutions was $3.68 \cdot 10^{-4}$ molar. The concentrations of hydrochloric acid and stannous chloride were constant. In order to avoid the influence of alcohol, its concentration was kept constant. The amount of alcohol added was the difference between the maximum amount of dimethylglyoxime used and the amount used in a given experiment. The volume of the solutions was 50 ml. The results of light absorption measurements for the solutions along the Section 1-2 are shown in Table 1.

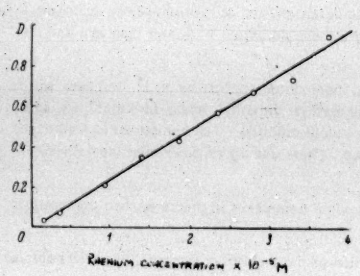

Fig. 1. Variation of light absorption of the solutions with rhenium concentration.

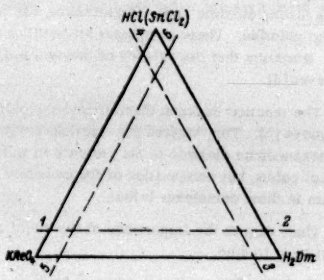

Fig. 2. The system: potassium perrhenate – dimethylglyoxime – hydrochloric acid. 1-2, 3-4, 5-6 are sections through the system.

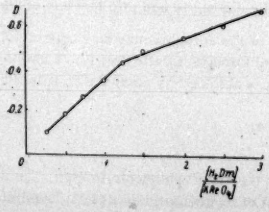

Fig. 3. Variation of optical density at constant potassium perrhenate concentration.

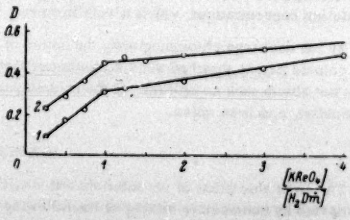

Fig. 4. Variation of optical density at constant dimethylglyoxime concentration. 1) $7.32 \cdot 10^{-5}$ M, 2) $9.2 \cdot 10^{-5}$ M.

Study of the light absorption of the solutions along the Section 3-4 is of some importance for the determination of the composition of the complex. In this series of experiments the rhenium concentration was constant at $7.32 \cdot 10^{-5}$ molar, and the concentration of dimethylglyoxime was varied (Fig. 3).

The light absorption of the solutions along the Section 5-6 was measured at constant dimethylglyoxime concentrations of $7.32 \cdot 10^{-5}$ and $9.2 \cdot 10^{-5}$ molar. The rhenium concentration was varied (Fig. 4).

For the determination of the valency of rhenium in the rhenium – dimethylgloxime complex, the light absorption of the system $KReO_4 – H_2Dm – SnCl_2$ (Fig. 2) along the 5-6 Section was studied; the hydrochloric acid and

TABLE 1

Light Absorption of Solutions

Amount (in ml)			
$KReO_4$	H_2Dm	alcohol	D
2.5	7.5	0.0	0.82
3.3	6.7	0.8	0.96
5.0	5.0	2.5	1.09
6.7	3.3	4.2	1.02
7.5	2.5	5.0	0.78

dimethylglyoxime concentrations were constant. The original potassium perrhenate and stannous chloride solutions were equimolecular. After the solutions were mixed, the color of the complex appeared, and its intensity decreased with time. Probably the oxidation products of alcohol or dimethylglyoxime reacted with stannous chloride or with reduced rhenium. Preliminary saturation of the solutions with carbon dioxide or sulfur dioxide, or the addition of hydroxylamine, had no effect, and the complex was again destroyed. The alcohol solution was replaced by a solution of dimethylglyoxime sodium salt or by a saturated solution of dimethylglyoxime in water, which was also unsuccessful. Thus, the valency of rhenium could not be determined by the methods [6, 7].

The behavior of the colored part of the rhenium – dimethylglyoxime complex with ion exchange resins was studied with the aid of anionite TM and the cationite Sulfocarbon K. 10 g of anionite TM with grain size 0.5 mm was placed in a beaker with water to swell it. After 4 hours the anionite suspension was transferred to an ion exchange column, in which the anionite was first converted into the OH-form.

An acid solution containing the colored rhenium – dimethylglyoxime complex was passed through an ion exchange column prepared in this manner. The filtrate had the color of the original solution, so that the rhenium complex is not absorbed by anionite TM.

10 g of Sulfocarbon K was swollen for 4 hours and then transferred to an ion exchange column, in which the Sulfocarbon K was converted into the H-form by treatment with 400 ml of 2 N hydrochloric acid solution. When the rhenium complex was passed through H-Sulfocarbon, it was absorbed. The first portions of the filtrate were colorless, and later the color of the filtrate was less intense than that of the original solution. After passage of the solution the column was washed with 100 ml of distilled water. The filtrate from the wash waters was colorless. The column was then again washed with hydrochloric acid solution (1:1). The filtrate had the color of the original solution, but more intense. It was difficult to remove the absorbed complex completely from Sulfocarbon K; this requires prolonged acid treatment of the Sulfocarbon K. The high absorbability of the complex makes it possible to increase its concentration considerably in a single passage through Sulfocarbon K in the H-form.

The molecule of the rhenium – dimethylglyoxime complex contains 1 molecule of dimethylglyoxime, as the maximum light absorption of the solution along the Section 1-2 is found at the ratio $[Re]:[H_2Dm] = 1:1$ (Table 1). A study of the light absorption of the solutions at constant potassium perrhenate concentration showed that the two branches in Fig. 3 intersect at the ratio $[KReO_4]:[H_2Dm] \approx 1$. The smooth course of the curve indicates dissociation of the complex in these conditions. A more abrupt inflexion in the curves is seen in Fig. 4. at $[KReO_4]:[H_2Dm] = 1$.

Dimethylglyoxime [8] has the properties of a weak acid, $K_1 = 8 \cdot 10^{-12}$. In the conditions for complex formation, when hydrochloric acid concentration is 2.5 N, the dissociation of dimethylglyoxime is suppressed; therefore a molecule of dimethylglyoxime enters the complex.

The agreement between the results under different experimental conditions shows that in the rhenium – dimethylglyoxime complex, the ratio $[Re]:[H_2Dm] = 1:1$.

Other complexes, of the type $Re(H_2Dm)_n$ and $Re_n(H_2Dm)$, where $n > 1$, are not formed in the experimental conditions used. If colorless complexes of this type were formed, the curves in Figures 3 and 4 would have a different form or would pass through maxima. The method of investigating the light absorption of the solutions did not reveal the valency of rhenium in its complex with dimethylglyoxime. It is known that in the potentiometric titration of rhenic acid by stannous chloride the first clear jump of potential corresponds to quinquevalent rhenium. Quinquevalent rhenium is unstable and after further reduction becomes quadrivalent [9].

In order to determine the valency of rhenium in the complex, two experiments were carried out, which differed in the sequence in which the solutions were mixed. In the first experiment, stannous chloride was added to solutions of hydrochloric acid and potassium perrhenate and the solution was allowed to stand 4 hours. At the end of that time an alcohol solution of dimethylglyoxime was added to the solutions and stirred; the light absorption

was measured after 20 minutes. The result was the same as after the usual sequence for mixing the solutions, as described above. Therefore the development of the color of the complex does not depend on the sequence in which the dimethylglyoxime and stannous chloride solutions are mixed. These experiments show that rhenium is present in the quadrivalent state in the complex. If the valency of rhenium in the complex was five, the light absorption of the system would depend on the sequence of mixing. The light absorption would be greater with the usual sequence.

The behavior of the complex with ionites indicates the colored portion to be a cation.

On the basis of the above data we consider that the composition of rhenium – dimethylglyoxime complex in an acid medium in the presence of stannous chloride is represented by the formulas:

$$[ReOH_2Dm]Cl_2 \text{ or } [Re(OH)_2H_2Dm]Cl_2.$$

The formation of the complex occurs according to the reaction:

$$2ReO_4^- + 3Sn^{2+} + 2H_2Dm + 12H^+ \rightleftharpoons 2[ReOH_2Dm]^{2+} + 3Sn^{4+} + 6H_2O. \quad (1)$$

The dissociation of the rhenium – dimethylglyoxime complex is represented as follows:

$$[ReOH_2Dm]^{2+} \rightleftharpoons ReO^{2+} + H_2Dm;$$

and its instability constant is given by:

$$K = \frac{[H_2Dm] \cdot [ReO^{2+}]}{[ReOH_2Dm^{2+}]}.$$

The value of the instability constant of the complex was calculated from the data in Table 2.

The concentration of the complex formed was determined by means of a calibration graph (Fig. 1). For construction of the graph, the dimethylglyoxime and stannous chloride concentrations were several tens of times greater than required for complex formation according to Equation (1). In such conditions dissociation of the complex is suppressed by the excess reagents.

TABLE 2

Equilibrium concentration C (M)			D	K · 10^{-4}	E · 10^3
ReO^{2+} C · 10^{-5}	H_2Dm C · 10^{-5}	$[ReOH_2Dm^{2+}]$			
6.91	1.39	$4.5 \cdot 10^{-6}$	0.098	2.13	6.4
6.53	2.85	$8.3 \cdot 10^{-6}$	0.189	2.24	5.1
6.23	4.39	$1.13 \cdot 10^{-5}$	0.265	2.42	7.0
5.91	5.91	$1.45 \cdot 10^{-5}$	0.346	2.41	7.0
5.53	7.38	$1.83 \cdot 10^{-5}$	0.439	2.23	7.1
5.31	8.99	$2.05 \cdot 10^{-5}$	0.490	2.33	7.0
4.98	12.3	$2.38 \cdot 10^{-5}$	0.575	2.58	7.1
1.42	6.96	$4.0 \cdot 10^{-6}$	0.092	2.43	6.8
2.93	6.61	$7.5 \cdot 10^{-6}$	0.166	2.60	6.5
5.96	5.96	$1.4 \cdot 10^{-5}$	0.335	2.54	7.0

The equilibrium concentrations of rhenium and dimethylglyoxime were determined as the difference between the original concentrations and concentrations of the rhenium – dimethylgloxime complex.

The value of the instability constant for the complex, according to our data is $2.39 \cdot 10^{-4}$.

The number of dimethylglyoxime molecules in the complex may be determined by the logarithmic graph method [10]. The expression for the instability constant, after transformation, takes the form:

$$\log \frac{[ReOH_2Dm^{2+}]}{[ReO^{2+}]} = -\log K + n \log [H_2Dm],$$

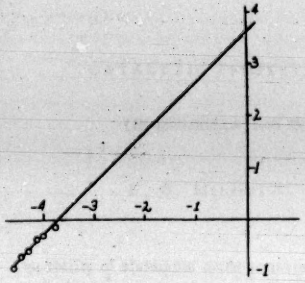

Fig. 5. Logarithmic graph.

where n is the number of H_2Dm molecules in the complex. The logarithmic graph (Fig. 5) is plotted in the coordinates

$$\log\frac{[ReOH_2Dm]^{2+}}{[ReO^{3+}]} - \log[H_2Dm].$$

The data for plotting this graph were taken from Table 2. The number n of dimethylglyoxime molecules within the inner sphere of the complex is equal to the tangent of the slope of the line relative to the abscissa axis. Figure 5 shows that the tangent of the slope is approximately equal to unity. Thus, the logarithmic graph method confirms that the complex contains 1 molecule of dimethylglyoxime.

The data of Table 2 were used to calculate the molar extinction coefficient by means of the formula $D = E \cdot C \cdot l$, were D is the optical density of the solution, C is the molar concentration of the complex and l is the length of the cell (in cm).

The mean value of the molar extinction coefficient is $6.9 \cdot 10^3$.

The literature [5] contains a value of 11 000 for the molar extinction coefficient. This discrepancy is probably explained by the fact that our measurements were carried out in the longer wave region of the spectrum and after a shorter time interval.

SUMMARY

1. The composition of the rhenium – dimethylglyoxime complex was studied by a physico-chemical method and by ion exchange chromatography.

2. The formula $[ReOH_2Dm]Cl_2$, is proposed for the complex formed in hydrochloric acid medium in the presence of stannous chloride.

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CATALYTIC PROPERTIES OF ACTIVATED ALUMINUM OXIDE

(IN ISOMERIZATION REACTIONS OF UNSATURATED HYDROCARBONS)

K. G. Miesserov, O. E. Morozova, and Al. A. Petrov

The ability of aluminum oxide activated by mineral acids to catalyze the isomerization of the olefin hydrocarbon chain has been reported in a number of papers [1-3].

While its isomerization effect is not inferior to that of aluminosilicate catalyst, activated aluminum oxide induces the hydrogen redistribution and cracking reactions to only a small extent, making it possible to bring about the catalytic isomerization of olefin hydrocarbons with b.p. > 200° [4]. However, though catalysts based on activated aluminum oxide are already being used in the petroleum industry [5], the nature of their catalytic activity remains unknown. The present work was devoted to a study of this question and also to an investigation of the effect of the activating acid anion on the catalyst properties.

The catalyst samples were prepared by mineral acid treatment of aluminum oxide in tablet form. The catalyst activity was determined from the yield of branched hydrocarbons from n-hexene and cyclohexene when they were brought into contact with the catalyst. Experiments at 300° and a volume rate of 0.6 liter/ liter hour showed that aluminum oxide, after being treated even with very dilute (0.01 N) hydrochloric acid, acquires appreciable catalytic activity, while treatment by 0.5-1.0 N solution yielded a catalyst which produced an equilibrium mixture of olefins in a single pass.

The effect of the activating acid anion on the catalyst activity can be seen from the data in Table 1 (1 volume of catalyst was treated with 10 volumes of 0.1 N acid solution).

As aluminum oxide treated with hydrochloric acid has the best selectivity in the isomerization of the olefin carbon chain, only this catalyst was used subsequently.

TABLE 1

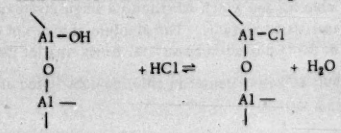
Catalyst treated with	Yield of branched hydrocarbons (in %) •	
	from hexene	from cyclohexene
HCl	47 (6)	85 (20)
HBr	31 (3)	63 (18)
HF	60 (21)	77 (39)
H_2SO_4	95 (20)	100 (43)
H_3PO_4	45 (2)	50 (6)
H_3BO_3	25 (1)	45 (6)
HNO_3	2 (nil)	4 (nil)
Original aluminum oxide	2 (nil)	5 (nil)

• The values are given as percentage of the monomer fraction. The parentheses show the weight percentages of the polymers formed.

The activity of catalysts of the given type is commonly associated with the presence of protons on their surface, and some workers consider that the protons are formed by molecular adsorption of the activating acid [1,2]. However, the experimental results of our work do not confirm this.

The treatment of 1 g of aluminum oxide with 100 ml of 0.008 N HCl during 3 hours resulted in the absorption of 45.2 mg-equivalents of chloride ions per 100 g of the dry catalyst.

After the addition of sodium chloride the amount of acid absorbed in the same conditions was 64.5 mg-equivalents per 100 g. Evidently the treatment of aluminum oxide with hydrochloric acid solution results in a reversible reaction according to the equation:



and the addition of sodium chloride shifts the equilibrium to the right. If molecular adsorption of the acid took

place, the introduction of sodium chloride would have the opposite effect of reducing the amount of acid absorbed.

Treatment of the chloro-substituted aluminum oxide with water or sodium acetate solution resulted in the appearance of acid in the solution, which can be attributed only to hydrolysis, as when the same sample was treated with sodium chloride solution no acidification took place, while molecularly adsorbed acid should have been evolved into sodium chloride solution also. No acid was formed when the catalyst was treated with silver nitrate solution, although a silver chloride precipitate was formed. This indicates that when aluminum oxide is treated with the acid, the sparingly soluble complex $Al_2O_3 \cdot HCl$ [6] is also not formed.

Thus, the treatment of aluminum oxide with hydrochloric acid results not in molecular adsorption of the latter, but in the replacement of the hydroxyl groups on the aluminum oxide surface by chloride ions.

Chloride ions were also absorbed when the specimens were treated with aluminum chloride solution. In this instance aluminum oxide reacted with bound hydrochloric acid, as was shown by the formation of basic salts of aluminum while its total content in the solution was unchanged.

The relationship between the chloride ion content of the samples and their catalytic activity was also studied.

A study of the effect of the acid concentration on the quantity of chloride ions taken up chemically by the samples showed that, if the acid is present in sufficient excess, the amount of chlorine which remained after the samples were heated at 300 and 600° did not depend on the activating acid concentration; therefore various degrees of saturation with chlorine were achieved by varying, together with the concentration of the acid used, also the duration of the treatment and the ratio between the sample and acid volumes.

TABLE 2

Sample No.	Heating temperature	Chlorine content (mg-equiv. per 100 g)	Yield of isomers (in %)
1	300°	46	26
2		53.5	41
3		66.5	50
4	600°	3.5	5.5
5		20.5	17
6		30.5	34
7		43.1	52

Table 2 shows the results of tests of the catalytic activity of aluminum oxide at different chlorine concentrations. The conversion of cyclohexene was carried out at 300° and a volume rate of 2.0 liter/liter hour.

The results in Table 2 show that the samples heated at 300° still contain considerable amounts of excess (inactive) chlorine; the chlorine content in Sample 1 is greater than in Sample 6, but the activity of the latter is higher; therefore a comparison of the activity and the chlorine content was possible only for samples heated at 600°, the catalytic effect of which is proportional to their chlorine content.

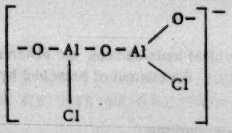
DISCUSSION OF RESULTS

In activation by means of hydrochloric acid, partial solution of aluminum oxide with the formation of aluminum chloride takes place first, and also the replacement of surface hydroxyl groups by chlorine. After decantation of the solution, some aluminum chloride remains in the catalyst. The aluminum chloride, which sublimes at 180°, is removed by heating; however, complete removal from a non-powered sample is achieved only at 600°.

The catalytic activity of aluminum oxide treated with hydrochloric acid is the result of the presence of chemically bound chloride ions on its surface. As was already pointed out, these can only appear as the result of a reaction between the surface hydroxyl groups and HCl. However, not every adsorbed chloride ion assists the formation of an active center. Aluminum ions in aluminum oxide may be combined with one or with two hydroxyl groups, according to their position in the lattice. In our opinion, aluminum oxide only acquires catalytic properties if a chloride ion replaces one of a pair of hydroxyl groups, while the hydrogen atom in the other hydroxyl group, owing to the proximity of electronegative chlorine, becomes mobile and capable of dissociation with the formation of a proton.

A chloride ion which substitutes a single hydroxyl group is apparently inactive, as was shown in the poisoning of the catalysts by pyridine. The absolute amounts of chemically sorbed pyridine (not removed by nitrogen blown through at 300°) proved to be several times smaller than the chlorine content of the same samples.

Thus, an active center in chlorine-substituted aluminum oxide may be represented as follows:



EXPERIMENTAL

The aluminum oxide was prepared by precipitation by means of ammonia from a solution of aluminum nitrate, followed by slow drying and molding of the gel. The aluminum oxide in tablet form was heated at 550-560°; its specific surface was 300 m^2/g, and it had no appreciable catalytic activity. The aluminum oxide was activated by holding 50 ml (35 g) of the catalyst 48 hours in 500 ml of mineral acid at room temperature. The solution was then decanted, and the catalyst dried first at 120°, and then in a furnace in a stream of nitrogen at 300°.

Chlorine in the chlorine-substituted aluminum oxide was determined by Volhard's method in an alkaline extract after treatment with 0.1 N NaOH. The accuracy of the determination is illustrated in Table 3.

TABLE 3

Experiment no.	Found in solution used for treating the aluminum oxide*		Chlorine found in the alkaline extract by Volhard's method
	hydrochloric acid (alkali titration)	chlorine (Volhard's method)	
1	32.8	31.5	32.0
2	65.7	64.0	65.0
3	99.2	98.0	98.5

* The values are given in mg-equiv. per 100 g of aluminum oxide.

The experiments detailed in Table 3 were performed as follows: 1 g weighed powdered samples were placed in conical flasks to which different volumes of 0.2 N HCl were added from a graduated pipet. At the same time the same volumes of the acid were added to 250 ml measuring flasks. The solutions in the measuring flasks were titrated with alkali with phenolphthalein indicator. The chlorine contents of these solutions were also determined by Volhard's method. The results were used to calculate the amount of chlorine supplied to the samples. At the end of two days the samples in the flasks were repeatedly treated with 0.1 N alkali solution. Portions of the solutions were decanted into 250 ml measuring flasks. The chlorine contents of the alkali extracts were determined by Volhard's method. A parallel blank experiment with the original aluminum oxide was also performed.

Poisoning of the samples was effected by pyridine in ether solution, after which the samples were placed in the catalytic furnace through which a stream of nitrogen was passed 10 hours at 300°. The residual pyridine in the samples was determined by treatment of the aluminum oxide with 15% alkali and determination of the pyridine driven off by titration with hydrochloric acid with bromophenol blue indicator [7]. The aluminum content in the solutions was determined by A. V. Sokolov's method [8].

The branched hydrocarbons in the products of catalytic treatment of n-hexene and cyclohexene were determined by making use of the different course of bromination of normal and branched olefins.

As was shown by one of the present authors, the bromination of olefins by means of Kaufmann's solution (0.1 N bromine solution in methanol saturated with sodium bromide) proceeds in two directions – with the formation of a dibromide and the formation of a methoxy monobromide with the evolution of hydrogen bromide, the latter being particularly significant for hydrocarbons of the type $R_1-\underset{\displaystyle R_2}{\overset{\displaystyle |}{C}}=CH-R_3$ [9].

0.1-0.2 ml of the mixture to be studied was added to 20 ml of Kaufmann's solution. Excess bromine was titrated with thiosulfate after the addition of 20 ml of 10% potassium iodide solution. 20 ml of 5% potassium iodate solution was then added immediately, and the iodine liberated was again titrated.

The amount of hydrobromic acid evolved (as molar percent of the total amount of reacted bromine) was calculated by means of the formula: $K=\frac{C}{A-B}\cdot 100$, where C is the number of milliliters taken in the second titration, B is the number of milliliters in the first titration, and A is the number of milliliters in a blank titration

of the bromine solution.

As, from bromination data for the individual hydrocarbons, the difference between K for branched hexene (2-methylpentene-2) and K for n-hexene was 13.5, the content of branched hydrocarbons in the mixture can be calculated by means of the formula:

$$\% \text{ isomers} = \frac{K_i - K_{n\text{-hexene}}}{13.5}$$

Mixtures of n-hexene and 2-methylpentene-2 (the main conversion product of n-hexene) were previously used to establish a direct dependence between the branched hydrocarbon content and the amount of hydrogen bromide evolved during bromination.

The above method of analysis is not strictly quantitative; however, with the use of a correction for the hydrogen bromide content of the original Kaufmann's solution the accuracy of the determination reaches 5%, which is not inferior to the accuracy of spectrometric analysis of such mixtures.

SUMMARY

1. The catalytic properties of aluminum oxide activated by mineral acids with respect to the carbon chain isomerization of olefinic hydrocarbons were studied.

2. The acids form the following sequence by their increasing activating effects: boric, hydrobromic, phosphoric, hydrochloric, hydrofluoric, sulfuric.

3. When aluminum oxide is treated with hydrochloric acid, hydroxyl groups on the aluminum oxide surface are replaced by chloride ions.

4. The activity of aluminum oxide treated with hydrochloric acid is in direct dependence on the amount of chemically bound chlorine.

5. A structural scheme for the active centers in activated aluminum oxide is put forward.

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MECHANISM OF THE GRIGNARD-WURTZ REACTION

I. SYNTHESIS OF SOME ALKYLAROMATIC HYDROCARBONS FROM BENZYL CHLORIDE, α-BROMOETHYLBENZENE, AND α-BROMO-α-METHYLETHYLBENZENE

M. S. Malinovsky and A. A. Yavorovsky

The purpose of this work was the synthesis of higher benzene homologs with branched side chains (C_{10}–C_{14}) which might also be of some interest in automobile fuel chemistry.

At the same time, we were also interested in studying the reactions between organomagnesium compounds (in particular, those with a tertiary structure) and halogen derivatives of aromatic hydrocarbons, in order to have the possibility of drawing conclusions concerning the mechanism of these reactions.

The halogenated derivatives used in the reactions with Grignard reagents were benzyl chloride, α-bromoethylbenzene, and α-bromo-α-methylethylbenzene, which show a regular change of structure. Of these halogenated derivatives, the reaction only of benzyl chloride with organomagnesium compounds has been described [1], and the reactions of the other two are described here for the first time; by their aid it proved possible to synthesize certain new hydrocarbons.

In the work every effort was made to isolate all the side-products of the reactions as completely as possible, as otherwise it is difficult to evaluate the reaction mechanism. Benzyl chloride was reacted with sec-butylmagnesium bromide, isoamylmagnesium bromide, tert-butylmagnesium chloride, and triethylmethanemagnesium chloride.

α-Bromoethylbenzene was reacted with ethylmagnesium bromide, isopropyl magnesium bromide, n- and sec-butylmagnesium bromide, triethylmethanemagnesium chloride, and benzylmagnesium chloride. α-Bromo-α-methylethylbenzene was reacted with ethylmagnesium bromide, isopropylmagnesium bromide, n- and isobutyl magnesium bromide, isoamylmagnesium bromide, and tert-butylmagnesium chloride.

The following rules were noted in the course of the work.

Benzyl chloride only reacts at 90° with the above Grignard reagents. The yields of normally condensed hydrocarbons (of the A – B type)* decrease (in the cases studied) from primary (average 30%) to tertiary radicals (average 20%). Hydrocarbons of the A – A and B – B type (average 20% of each), polymeric products (up to 10%) and toluene are also formed. In addition, the reaction between benzyl chloride and Grignard reagents containing tertiary radicals resulted in the formation of high-boiling hydrocarbons, with a tentative formula of the type $C_6H_5CH_2-C_6H_4-CH_2C_6H_5$.

The yields of normally condensed hydrocarbons decrease in the transition from benzyl chloride to α-bromoethylbenzene, even with primary radicals in the organomagnesium compounds. For example, in the condensation with ethylmagnesium bromide at the boiling point of ether no hydrocarbon of the type A – B is formed at all, and at 110° its yield is only 8%. Organomagnesium compounds with tertiary radicals do not react with $C_6H_5CHBrCH_3$ even at 110°.

The nature of the reactions between α-bromo-α-methylethylbenzene and Grignard reagents differs from those of the halogen derivatives discussed above. In this instance the reaction is very rapid, and takes place even at the boiling point of ether, with the formation of normal condensation products (of the A – B type) in fairly good yields. It is interesting to note that the reaction between α-bromo-α-methylethylbenzene and ethylmagnesium bromide proceeded even at −40°, and the yield of the hydrocarbon reached 63%, instead of the 34% obtained by the same reaction in boiling ether.

EXPERIMENTAL

α-Bromoethylbenzene [b.p. 63–64° (2 mm) n_D^{20} 1.5470, d_4^{20} 1.3472] [2], and α-bromo-α-methylethylbenzene [b.p. 45–46° (residual pressure 10^{-2} – 10^{-3}), n_D^{20} 1.528, d_4^{20} 1.2850] were prepared from hydrogen bromide and styrene

* A is the radical in the organomagnesium compound, and B is the radical in the halogenated hydrocarbon.

or methylstyrene respectively.

Pure α-bromo-α-methylethylbenzene is not described in the literature.

	Found %:	C 54.60; H 5.42; Br 39.77
$C_9H_{11}Br$.	Calculated%:	C 54.26; H 5.56; Br 40.13

Triethylchloromethane was prepared from triethyl carbinol [3], and the latter was prepared from ethylmagnesium bromide and diethyl carbonate [4].

The organomagnesium compounds were prepared by the usual method from 0.25 mole of the halogenated derivative. A solution of the Grignard reagent was filtered through a porous glass plate into a similar apparatus and analyzed [5]. The amounts of benzyl chloride, α-bromoethylbenzene, and α-bromo-α-methylethylbenzene taken were based on consideration of the analytical data. After addition of the second component the mixture was boiled another hour. The ether was then driven off, the residue was heated in xylene on the boiling water bath several hours to a negative reaction with Michler's ketone. The mixture was cooled and decomposed by being poured into ice-water acidified with sulfuric acid, and extracted with ether. The ether extracts were washed with soda solution and with water, dried by calcium chloride, and the ether was driven off. The residue was kept twenty-four hours in a vacuum desiccator at 400-500 mm over paraffin. The products were separated by means of vacuum, high vacuum, and molecular distillation, freezing, recrystallization, fractionation over a high-efficiency column, and in some instances chromatographically (in the vapor phase).

The hydrocarbons obtained were identified by their boiling and melting points, refractive indices, molecular weights, elementary analysis data, and by destructive oxidation.

The experimental results and the conditions for the reactions between halogenated hydrocarbons and organomagnesium compounds are shown in Tables 1, 2, and 3.

In the reactions of C_2H_5MgBr and C_4H_9MgBr with α-bromoethylbenzene, the formation of saturated and unsaturated hydrocarbons was observed.

The physical constants of the hydrocarbons formed are shown in Table 4.

The investigated reactions between halogenated hydrocarbons and organomagnesium compounds resulted in the formation of 4 hydrocarbons not previously described, analyses of which are given below.

1-Phenyl-2,2-diethylbutane, a colorless liquid with a pleasant terpene odor. B.p. 112-115° (15 mm), d_4^{20} 0.867, n_D^{20} 1.4995.

	Found %:	C 88.67; H 11.60; M 182.
$C_{14}H_{22}$.	Calculated%:	C 88.42; H 11.58; M 190.

p-Benzylneopentylbenzene, a colorless liquid with an odor of aromatic compounds. B.p. 187-190° ($^1/_2$ mm), d_4^{20} 1.052, n_D^{20} 1.572.

	Found %:	C 91.25; H 8.88; M 242.4.
$C_{18}H_{22}$.	Calculated%:	C 90.75; H 9.25; M 238.

2-Phenyl-3-methylpentane. B.p. 110-112° (10 mm), d_4^{20} 0.862, n_D^{20} 1.4890.

	Found %:	C 89.50; H 11.12.
$C_{12}H_{18}$.	Calculated%:	C 89.40; H 11.10.

2-Phenyl-2,3-dimethylbutane. B.p. 197-200° (746 mm), d_4^{20} 0.878, n_D^{20} 1.4945.

	Found %:	C 89.37; H 11.00; M 168.1.
$C_{12}H_{18}$.	Calculated%:	C 88.88; H 11.12; M 162.

In addition, the reaction between benzyl chloride and triethylmethanemagnesium chloride yielded a higher hydrocarbon with the composition $C_{21}H_{28}$, the structure of which was not established. B.p. 203-206° ($^1/_2$ mm), d_4^{20} 1.040, n_D^{20} 1.587.

	Found %:	C 90.30; H 9.92; M 295.
$C_{21}H_{28}$.	Calculated%:	C 90.00; H 10.00; M280.

TABLE 1

Hydrocarbons Obtained by Reactions of Benzyl Chloride with RMgX

RMgX	Reaction conditions	Hydrocarbons formed: type A-B	type A-A	type B-B (dibenzyl)	other hydrocarbons
iso-$C_6H_{11}MgBr$	9 hours heating at 90°	$C_6H_5CH_2C_5H_{11}$-iso, 33%	2,7-Dimethyloctane 21.7%	20%	$C_6H_5CH_3$, 5% $C_6H_5CH_2C_6H_4(CH_2)_2C_6H_5$, 70% Residue 13%
$CH_3CHC_2H_5$ | MgBr	4 hours heating at 90°	$C_6H_5CH_2CH(CH_3)C_2H_5$, 30%	2,3-Dimethylhexane 10.7%	20%	C_6H_5CH Residue 38.3%
$(CH_3)_3CMgCl$	1 hour heating at 90°	$C_6H_5CH_2C(CH_3)_3$, 24%	–	28.7%	$C_6H_5CH_3$, 26.5% $C_{18}H_{22}$, 8.8% Residue 11.8%
$(C_2H_5)_3CMgCl$	Ditto	$C_6H_5CH_2C(C_2H_5)_3$, 19.6%	Mixture of 3-ethyl-pentane and 3-ethyl-pentene 22.9%	20.3%	$C_6H_5CH_3$, 2.9% Higher hydrocarbons $C_{21}H_{28}$, 8.7% Residue 11.2%

TABLE 2

Hydrocarbons Obtained by Reactions of α-Bromoethylbenzene with RMgX

Experiment No.	RMg X	Reaction conditions	Hydrocarbons formed • type A-B	type A-A
1	C_2H_5MgBr	a) 1 hour at 35° b) at 105-110° in xylene	$C_6H_5CH(CH_3)-C_2H_5$, 8%	–
2	n-C_4H_9MgBr	1 hour at the boil	$C_6H_5CH(CH_3)-C_4H_9$, 25%	$CH_3(CH_2)_6CH_3$, 6%
3	$CH_3-CH-C_2H_5$ | MgBr	See Experiment 2	$C_6H_5CH(CH_3)CH(CH_3)C_2H_5$, 4%	3,4-Dimethylhexene, 20%
4	$(CH_3)_3CMgCl$	See Experiment 2	–	$(CH_3)_3C-C(CH_3)_3$, 43%
5	$C_6H_5CH_2MgCl$	See Experiment 2	$C_6H_5CH(CH_3)-CH_2C_6H_5$, 20%	$C_6H_5CH_2-CH_2C_6H_5$, 44%

• In all experiments 2,3-diphenylbutane, ethylbenzene, and styrene were formed. In Experiments 2-5 some α-bromoethylbenzene was obtained unchanged.

TABLE 3

Hydrocarbons Obtained by Reactions of α-Bromo-α-methylethylbenzene with RMgX

Experiment No.	RMgX	Reaction conditions	Hydrocarbons formed •	
			type A-B	type A-A
1	C_2H_5MgBr	a) slow boiling, 2 hours	$C_6H_5C(CH_3)_2C_2H_5$, 34%	–
		b) at −40°	The same, 63%	–
2	$(CH_3)_2CHMgBr$	With slow boiling	$C_6H_5C(CH_3)_2CH(CH_3)_2$, 26.5%	–
3.	iso-C_4H_9MgBr	In conditions of the previous expetiment	$C_6H_5(CH_3)_2-C_4H_9$-iso, 18.3%	–
4.	n-C_4H_9MgBr	In conditions of Experiment 2	$C_6H_5C(CH_3)_2-C_4H_9$-n, 27%	–
5	$(CH_3)_3CMgCl$	In conditions of Experiment 2	–	$(CH_3)_3C-C(CH_3)_3$, 45%
6	iso-$C_5H_{11}MgBr$	In conditions of Experiment 2	$C_6H_5C(CH_3)_2C_5H_{11}$-iso, 9.2%	2,7-Dimethyloctane, 16.6%

TABLE 4

Physical Properties of the Hydrocarbons Formed ••

Serial No.	Hydrocarbons	b.p.	m.p.	d_4^{20}	n_D^{20}	References
1	$C_6H_5CH_2-CH_2-C_6H_5$	—	52°	—	—	[6, 7]
2	$(CH_3)_2CH-(CH_2)_4-CH(CH_3)_2$	155—158°	—	0.722	1.413	[7]
3	$C_6H_5CH_2-CH_2-CH_2-CH(CH_3)_2$	209—213	—	0.854	1.485	[8]
4	$C_6H_5CH_2-C_6H_4-CH_2-CH_2C_6H_5$	226—229 (10 mm)	—	1.038	1.590	[9]
5	$C_6H_5CH_3$	105—110	—	0.869	1.4955	[6]
6	$C_6H_5CH_2C(CH_3)_3$	185—186	—	0.857	1.4823	[10]
7	$CH_3CH_2CH(CH_3)CH(CH_3)CH_2CH_3$	113—116	—	1.719	1.404	[7]
8	$C_6H_5CH_2CH(CH_3)(C_2H_5)$	100—102 (15 mm)	—	0.863	1.487	[11]
9	$C_6H_5CH(CH_3)(C_2H_5)$	171—173	—	0.860	1.485	[13, 15, 18]
10	$CH_3-(CH_2)_6-CH_3$	123—124	—	0.700	—	[6]
11	$C_6H_5CH(CH_3)(C_3H_7)$	208—212	—	0.861	1.490	[14]
12	$(CH_3)_3C-C(CH_3)_3$	—	102			[7]
13	$C_6H_5CH(CH_3)-CH_2C_2H_5$	276	—	0.980	1.560	[6, 18]
14	$C_6H_5C(CH_3)=CH_2$	163—166	—	—	—	[6, 7]
15	$C_6H_5C(CH_3)(C_2H_5)$	78—81 (15 mm)	—	0.875	1.495	[17]
16	$C_6H_5C(CH_3)_2CH_2CH(CH_3)_2$	100—102 (15 mm)	—	0.870	1.501	[19]
17	$C_6H_5C(CH_3)_2(CH_2)_2-CH_3$	226—227	—	0.880	1.495	[11]
18	$C_6H_5C(CH_3)_2(CH_2)_3CH(CH_3)_2$	118—120 (15 mm)	—	0.883	1.501	[19]
19	$C_6H_5CH(CH_3)-CH(CH_3)C_6H_{11}$, and also the D,L isomer	140 (10 mm)	126 8	0.9756	1.555	[12, 6]

• In all experiments 2,3-diphenyl-2,3-dimethylbutane, methylstyrene, and cumene were formed.

•• Except those synthesized for the first time.

SUMMARY

1. The reactions between a series of organomagnesium compounds and benzyl chloride, α-bromoethylbenzene, and α-bromo-α-methylethylbenzene have been studied; practically all the individual reaction products have been isolated and identified.

2. 4 new hydrocarbons not described in the literature were obtained: 1-phenyl-2,2-diethylbutane, p-benzyl--neopentylbenzene, 2-phenyl-3-methylpentane, and 2-phenyl-2,3-dimethylbutane.

3. The nature of the reaction with organomagnesium compounds varies in the series $C_6H_5CH_2Cl$, $C_6H_5CHBrCH_3$ and $C_6H_5CBr(CH_3)_2$: the yields of normal condensation products (type A-B) increase in the transition from α-bromoethylbenzene to α-bromo-α-methylethylbenzene.

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IODINATION OF VINYL ACETATE

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The literature does not describe any methods for the iodination of vinyl acetate, which is an acidophobic substance. Our experiments showed that elementary iodine reacts violently with this ester with the formation of a tarry mass from which any individual iodine-containing substance cannot be isolated. An attempt to bring iodination about by means of dioxane diiodide, first prepared and described by A. E. Favorsky [1] also did not give satisfactory results. A. P. Terentyev, L. I. Velenky and L. A. Yanovskaya [2] successfully used dioxane chloroiodide, but, as these authors point out, the iodination was carried out in pyridine. Evidently the iodinating agent in this instance was pyridine chloroiodide, as pyridine always displaces dioxane from its complex compounds.

We have shown that vinyl acetate can be iodinated fairly well by means of pyridine diiodide(a complex compound of pyridine with iodine) in the presence of small amounts of NaI or KI, the iodine being added at the vinyl radical double bond. In all probability the iodination of vinyl acetate is an ionogenic process. It is known that the iodine molecule acts in the dissociated form in many reactions. When iodine reacts with pyridine, which is not only a solvent but a donor-type complex former, the dissociation of the iodine molecule into charged particles is intensified. The complex $[C_5H_5NI]^+$ cation is the active ion which initiates the reaction with the vinyl acetate molecule. The catalytic effect of NaI or KI should apparently be attributed to the fact that an increase of I^- ion concentration favors the more rapid conversion of the unstable $CH_3-COO-\overset{+}{C}H-CH_2I$ into the stable diiodide molecule. On these grounds the iodination of vinyl acetate may be represented by the following schemes:

$$I_2 \rightleftharpoons I^+ + I^- + C_5H_5N \longrightarrow [C_5H_5NI]^+ I^-;$$

$$CH_3-COO-CH=CH_2 \dashrightarrow CH_3-COO-\overset{+}{C}H-\overset{-}{C}H_2 + [C_5H_5NI]^+ \dashrightarrow CH_3-COO-\overset{+}{C}H-CH_2I + C_5H_5N;$$

$$CH_3-COO-\overset{+}{C}H-CH_2I + I^- \dashrightarrow CH_3-COO-CHI-CH_2I.$$

EXPERIMENTAL

Preparation of pyridine diiodide. 6.7 ml of dry pyridine was added dropwise to a solution of 21.3 g of crystalline iodine in 200 ml of anhydrous ether. After removal of the ether, shiny orange crystals, m.p. 59-60° were precipitated. The yield was 28 g. To avoid volatilization, pyridine diiodide should be kept in a firmly closed vessel.

Iodination of vinyl acetate. 6.7 g of pyridine diiodide was mixed with 2 ml of pyridine and 0.15 g of sodium iodide. 3.5 ml of freshly distilled vinyl acetate (b.p. 73°, n_D^{20} 1.3958) was added dropwise to the mixture with stirring and cooling (10-12°). Deep violet crystals were formed after 30 minutes. The crystals were washed with sodium thiosulfate solution and then with water, and dried in a vacuum desiccator over sulfuric acid. The yield was 7 g (51.4%, calculated on the vinyl acetate). M.p. 125°.

	Found %:	I 74.70.
$C_4H_6O_2I_2$.	Calculated %:	I 74.70.
	Found:	M 333.30 (Rast)
$C_4H_6O_2I_2$.	Calculated:	M 340.07.

SUMMARY

Vinyl acetate was iodinated by means of pyridine diiodide. The product was α,β-diiodoethyl acetate.

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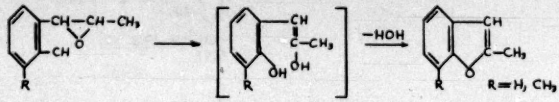
INVESTIGATIONS OF OXIDO (EPOXY) COMPOUNDS

VI. PROPERTIES OF α-OXIDES OF ALLYL AND PROPENYL DERIVATIVES OF m- and p-CRESOLS AND OF GUAIACOL

V. I. Pansevich-Kolyada and Z. B. Idelchik

In a study of the properties of α-oxides of allyl and propenyl derivatives of phenol and o-cresol it was established [1] that these compounds differ considerably from the α-oxides of ethylene hydrocarbons. The differences between the α-oxides of allyl derivatives of phenol and o-cresol and the α-oxides of propenyl derivatives of the same phenols are just as great.

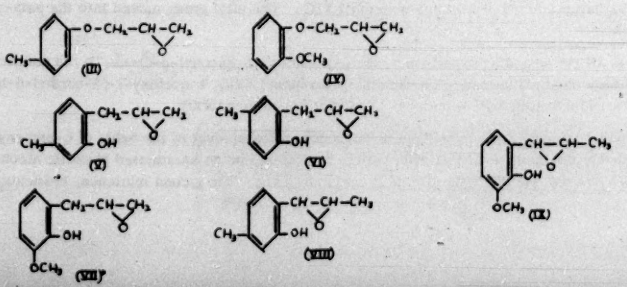
The oxide ring of the α-oxides of allylphenols is inert. It does not react with acetic anhydride and remains unchanged by the action of anhydrous zinc chloride. On the contrary, the oxide ring of propenylphenol α-oxides is very unstable. These substances form benzofurane derivatives by the action of acetic anhydride, upon distillation, and during storage in a desiccator over sulfuric acid at room temperature. Such transformations of propenylphenol oxides can be attributed only to their preliminary isomerization to unsaturated phenolic alcohols, which are very readily dehydrated with the formation of coumarone derivatives:



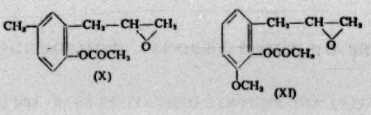
In the present investigation the properties of the α-oxides of allyl and propenyl derivatives of m- and p-cresol and of guaiacol were studied. It was found that the oxides of allyl and propenyl derivatives of m- cresol, and also of the allyl derivatives of p-cresol and guaiacol (o-eugenol) are similar to the oxides of the same derivatives of phenol and o-cresol [1]. The oxides of o-propenyl-p-cresol and o-methoxy-o-propenylphenol (o-isoeugenol), however, differ considerably from the oxides of the propenyl derivatives of all the other phenols.

We used the Claisen reaction [2] to synthesize the allyl ethers of m-cresol (I), p-cresol, and guaiacol. Rearrangement of these ethers yielded o-allyl-m-cresol, o-allyl-p-cresol, and o-methoxy-o-allylphenol (o-eugenol). Isomerization of the latter yielded o-propenyl-m-cresol, o-propenyl-p-cresol (II), and o-methoxy-o-propenylphenol (o-isoeugenol).

The allyl ethers of p-cresol and guaiacol, and also the allyl derivatives of m-cresol, p-cresol, and guaiacol, and the propenyl derivatives of m-cresol and guaiacol, were oxidized by acetyl hydroperoxide to give the corresponding oxides: 1-(p-tolyloxy)-oxide-2,3-propane (III), 1-(o-methoxyphenoxy)-oxide-2,3-propane (IV), 3-methyl-6-(2,3-oxidopropyl)-phenol (V), 4-methyl-2-(2,3-oxido-propyl)-phenol (VI), 2-methoxy-6-(2,3-oxidopropyl)-phenol (VII), 3-methyl-6-(1,2-oxidopropyl)-phenol (VIII), and 2-methoxy-6-(1,2-oxidopropyl)-phenol (IX):



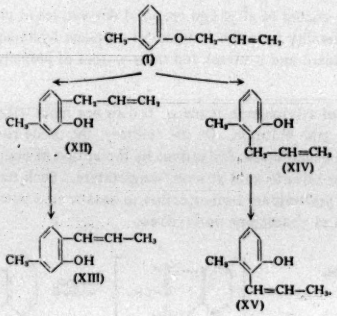
The oxides of o-allyl-p-cresol (VI) and o-methoxy-o-allylphenol (o-eugenol) (VII), like the oxides of allylphenol and o-allyl-o-cresol react with acetic anhydride to give the acetoxy compounds 1-methyl-4-acetoxy-3-(2,3-oxidopropyl)-benzene (XI):



(X) (XI)

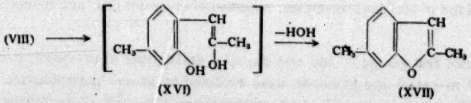
The action of acetic anhydride on the oxide of o-allyl-m-cresol (V) was not studied owing to shortage of the substance.

The allyl and propenyl derivatives of m-cresol may exist in two isomeric forms according to the rearrangement of the allyl ether (I):



We could not find any information in the literature as to which isomer is formed in this reaction [3]. We expected the formation of the isomers (XII) and (XIII), the molecules of which are more symmetrical and the formation of which is not subject to any steric hindrances, and this was confirmed experimentally.

The oxide of o-propenyl-m-cresol (VIII), like the oxides of propenyl derivatives of phenol and o-cresol [1], when stored in a desiccator over sulfuric acid, is converted into 2,6-dimethylbenzofuran (XVII) owing to enolization of the oxide ring followed by dehydration of the intermediate unsaturated phenolic alcohol (XVI), according to the scheme:



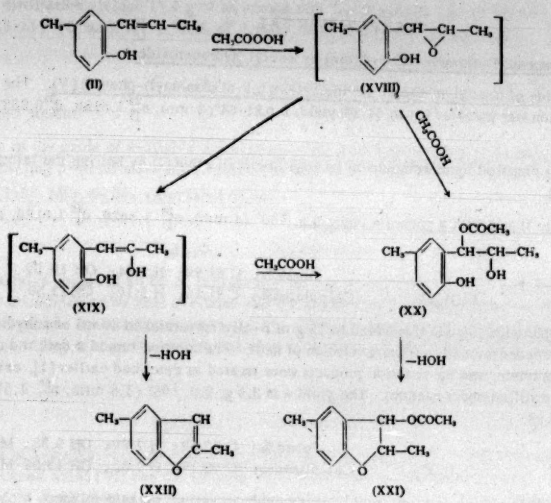
(XVI) (XVII)

The formation of 2,6-dimethylbenzofuran confirms the structure of the allyl and propenyl derivatives of m-cresol (XII and XIII). Rearrangement of m-cresol allyl ether led to the formation of o-allyl-m-cresol (XII), while isomerization of the latter yielded o-propenyl-m-cresol (XIII). The allyl group moved into the para-position relative to the methyl.

In contrast to all the preceding experiments, the oxidation of o-propenyl-p-cresol (II) did not yield an oxide. Three compounds were obtained instead: 2,5-dimethylbenzofuran (XXII), 1-acetoxy-1-(3-methyl-6-hydrophenyl)-propanol-2- (XX), and 2,5-dimethyl-3-acetoxy-2,3-dihydrobenzofuran (XXI).

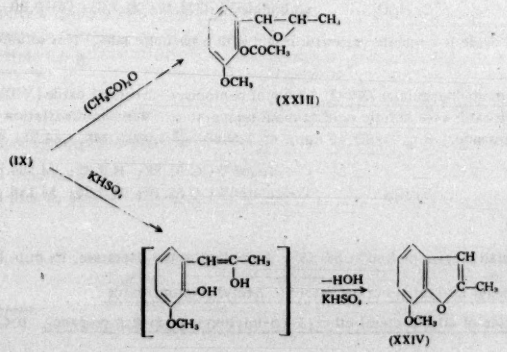
2,5-Dimethylbenzofuran (XXII) is, without doubt, a conversion product of the oxide of o-propenyl-p-cresol (XVIII). Most probably the latter was isomerized during distillation into an unsaturated phenolic alcohol (XIX) which because of easy dehydration, yielded a substituted benzofuran (XXII). The second substance, 1-acetoxy-1-(3-

-methyl-6-hydroxyphenyl-propanol-2 (XX) could have been formed by one of the following possible routes: acetylation of the oxide of o-propenyl-p-cresol (XVIII), or addition of acetic acid to the phenolic alcohol (XIX). Finally, 2,5-dimethyl-3-acetoxy-2,3-dihydrobenzofuran (XXI), is undoubtedly the dehydration product of the phenolic glycol monoacetate (XX). All these conversions may be represented by the following scheme:



The formation of an acetylated derivative of dihydrobenzofuran (XXI) is a convincing confirmation of the structure of the phenolic glycol monacetate (XX).

Special mention must be made of the oxide of o-isoeugenol (IX) which differed considerably from the oxides of all the other propenyl derivatives of phenols. The latter form coumarone derivatives when boiled with acetic anhydride, while o-isoeugenol oxide (IX) is acetylated in these conditions, like the allyl phenol oxides, at the phenolic hydroxyl group and forms an oxido acetate, 1-methoxy-2-acetoxy-3-(1,2-oxidopropyl)-benzene (XXIII). However, when the oxide (IX) was heated 6 hours on the boiling water bath with potassium bisulfate, 2-methyl--7-methoxybenzofuran (XXIV) was formed. The transformations of o-isoeugenol oxide (IX) occur according to the following scheme:



This difference between the α-oxide of propenylguaiacol (IX) and other oxides similar to it is undoubtedly caused by the influence of the methoxy group. Most probably this influence affects not the oxide ring, but the adjacent phenolic hydroxyl, hindering the removal of a hydrogen atom from it. This gives reason to suppose that the furan ring is formed with the aid of the oxygen atom from the phenolic hydroxyl, and not from the oxide ring. The oxygen of the oxide ring is used in the formation of the water molecule split off.

EXPERIMENTAL

Oxidation of Allyl and Propenyl Derivatives of m-Cresol by Acetyl Hydroperoxide.

Preparation of the oxide of o-allyl-m-cresol (3-methyl-6-(2,3-oxidopropyl)-phenol) (V). The m-cresol allyl ether (I) used for this reaction was prepared [2] in 51.2% yield. B.p.81-84°(3 mm), n_D^{20} 1.5180, d_4^{20} 0.9687, MR_D 46.30; calculated 45.95.

o-Allyl-m-cresol was prepared by rearrangement of allyl m-cresol ether (I) by boiling the latter 3 hours in a steam of carbon dioxide [2].

It is a colorless mobile liquid with a phenolic odor. B.p. 100° (4 mm), n_D^{20} 1.5420, d_4^{20} 1.0180, MR_D 45.66; calculated 45.87.

	Found %:	C 81.90; H 8.54; OH 10.32.
$C_{10}H_{12}O$.	Calculated%:	C 81.10; H 8.10; OH 11.50.

8.6 g of acetyl hydroperoxide (95.3%) was added to 15 g of o-allyl-m-cresol in 40 ml of anhydrous ether at 20-25°. The oxidation proceeded smoothly without evolution of heat. The solution turned a dark red color. After 2 days the oxidation was complete, and the reaction products were treated as described earlier [1], extracted with ether, dried by $MgSO_4$ and distilled under vacuum. The yield was 3.5 g. B.p. 108° (1.5 mm), n_D^{20} 1.5510, d_4^{20} 1.1365, MR_D 46.04; calculated 45.88.

	Found %:	C 73.53; H 7.30; OH 9.33. M 165.6; 170.8
$C_{10}H_{12}O_2$.	Calculated%:	C 73.17; H 7.31; OH 10.36 M 164.

o-Allyl-m-cresol oxide is a thick dark red liquid. It is soluble in various organic solvents.

Preparation of the oxide of o-propenyl-m-cresol (3-methyl-6-(1,2-oxidopropyl)-phenol (VIII). o-Propenyl-m-cresol was prepared by the isomerization of o-allyl-m-cresol by heating the latter in a solution of caustic potash in methyl alcohol [4, 5]. B.p. 99° (4 mm), n_D^{20} 1.5492, d_4^{20} 1.0185, MR_D 46.24; calculated 45.84.

4.3 g of acetyl hydroperoxide (95.3%) was added to 8.0 g of o-propenyl-m-cresol in 20 ml of anhydrous ether at 20-25°. The oxidation was very vigorous with much evolution of heat. The color of the solution changed from pale yellow to bright red. After 2 days the reaction products were treated as in the preceding experiment. Some decomposition took place when the oxidation products were distilled under vacuum. The yield was 3.0 g. B.p. 135-140° (5 mm), n_D^{20} 1.5455, d_4^{20} 1.1074, MR_D 45.79; calculated 45.88.

	Found %:	C72.08; H 7.48; OH 9.10; M 182.2, 179.7.
$C_{10}H_{12}O_2$.	Calculated%:	C73.17; H 7.31; OH10.30. M 164

o-Propenyl-m-cresol oxide is a mobile yellowish liquid with a phenolic odor. It is soluble in various organic solvents.

Preparation of 2,6-dimethylbenzofuran (XVII). 2.0 g of p-propenyl-m-cresol oxide (VIII) was dehydrated by leaving it 48 hours in a desiccator over sulfuric acid at room temperature. Vacuum distillation of the dehydration product yielded 1.0 g of substance. B.p. 72-82° (5 mm), n_D^{20} 1.5480, d_4^{20} 1.0325, MR_D 44.91; calculated 43.75.

	Found %:	C 81.88; H 7.36; M 134.8, 142.0.
$C_{10}H_{10}O$.	Calculated%:	C 82.19; H 6.85; M 146.

No active hydrogen present.

2,6-Dimethylbenzofuran picrate melted at 56-58°. According to the literature, its m.p. is 58-59° [6].

Oxidation of Allyl and Propenyl Derivatives of p-Cresol by Acetyl Hydroperoxide.

Preparation of the oxide of allyl p-cresol ether (1-(p-tolyloxy)-oxido-2,3-propane). p-Cresol was prepared

by the sulfonation of toluene followed by saponification of the p-toluene sulfonic acid [7]. The allyl ether of p-cresol was synthesized with 80% yield. B.p. 102° (17 mm), n_D^{20} 1.5204, d_4^{20} 0.9726, MR_D 46.23; calculated 45.96.

40 g of p-cresol allyl ether in 80 ml of anhydrous ether was oxidized by 22.2 g of acetyl hydroperoxide (92%). The oxidation proceeded slowly, without evolution of heat. The color of the solution became first yellow and then orange. The oxidation was complete after 12 days. The reaction products were treated as in the preceding experiments. Vacuum distillation yielded 17.0 g of an orange oily liquid with an odor of tobacco, soluble in various organic solvents. B.p. 115-117° (5 mm), n_D^{20} 1.5258, d_4^{20} 1.0831, MR_D 46.46; calculated 46.00.

	Found %:	C 73.33; H 7.82; M 167.8, 166.5.
$C_{10}H_{12}O_2$.	Calculated%:	C 73.17; H 7.32; M 164.

No active hydrogen present.

Preparation of the oxide of o-allyl-p-cresol (4-methyl-2-(2,3-oxidopropyl)-phenol) (VI). o-Allyl-p-cresol was prepared by boiling p-cresol allyl ether 14 hours at 200° in a stream of CO_2. Yield 88%. B.p. 79-80° (2 mm), n_D^{20} 1.5405, d_4^{20} 1.0120, MR_D 46.00; calculated 45.84.

	Found %:	C 81.33; H 8.38;
$C_{10}H_{12}O$.	Calculated%:	C 81.08; H 8.10.

40 g of o-allyl-p-cresol in 80 ml of anhydrous ether was oxidized by 22.2 g of acetyl hydroperoxide (92%). The reaction was accompanied by heat evolution and the color of the solution changed to orange. After 3 days no hydroperoxide was present in the reaction mixture. The oxidation products were treated in the usual way. Vacuum distillation yielded 17.0 g of a yellow oily liquid. B.p. 129° (4 mm), n_D^{20} 1.5485, d_4^{20} 1.1307, MR_D 46.12; calculated 45.88.

	Found %:	C 73.43; H 7.14. M 156, 168.7.
$C_{10}H_{12}O_2$.	Calculated%:	C 73.17; H 7.32; M 164.

Preparation of 1-methyl-4-acetoxy-3-(2,3-oxidopropyl)-benzene (X). 10 g of acetic anhydride was added to 3 g of o-allyl-p-cresol oxide (VI) and the mixture was boiled 4 hours. The acetic anhydride was driven off under vacuum, and twofold distillation of the reaction product yielded 1.0 g of a mobile colorless liquid with a sharp odor. B.p. 160° (13 mm), n_D^{20} 1.5200, d_4^{20} 1.1510, MR_D 55.14 · calculated 55.24.

	Found %:	C 70.00; H 6.68. M 197.9, 199.8.
$C_{12}H_{14}O_3$.	Calculated%:	C 70.00; H 6.79. M 206.

No active hydrogen present.

Oxidation of o-propenyl-p-cresol. o-Propenyl-p-cresol was prepared by the isomerization of o-allyl-p-cresol by the action of heat on the latter in a solution of caustic potash in methyl alcohol [4, 5]. B.p. 101-106° (4 mm), n_D^{20} 1.5688, d_4^{20} 1.0230, MR_D 47.70; calculated 45.84.

20 g of acetyl hydroperoxide (97%) was added to 37 g of o-propenyl-p-cresol in 80 ml of anhydrous ether at 20-25°. The oxidation proceeded very vigorously. After 2 days the reaction products were treated in the usual way. After the ether was removed, crystals were deposited which were insoluble in benzene and isoamyl acetate, and dissolved with great difficulty in dioxane. The crystals were filtered off and washed with isoamyl acetate; m.p. 143° (in sealed capillary). Yield 1.0 g.

	Found %:	C 64.59; H 7.64.
$C_{12}H_{16}O_4$.	Calculated%:	C 64.28; H 7.14.

The analytical data agree with 1-acetoxy-1-(3-methyl-6-hydroxyphenyl)-propanol-2 (XX).

The filtrate after removal of the crystals yielded two substances by twofold vacuum distillation. One was a mobile colorless liquid with an odor of coumarone derivatives. B.p. 77° (5 mm), n_D^{20} 1.5469, d_4^{20} 1.0328, MR_D 44.82; calculated 43.75.

	Found %:	C 81.31; H 7.50; M 136.5, 137.2.
$C_{10}H_{10}O$.	Calculated%:	C 82.19; H 6.85; M 146.

No active hydrogen present.

The picrate melted at 70-72°.

The analytical data agree with 2,5-dimethylbenzofuran (XXII) [6].

The other substance was a thick yellowish liquid with a sour odor. B.p. 140° (4 mm), n_D^{20} 1.5425, d_4^{20} 1.1241, MR_D 57.71; calculated 55.31.

Found %: C 70.27; H 7.20; M 190.5, 187.6.
$C_{12}H_{14}O_3$. Calculated%: C 70.00; H 6.79; M 206.

The picrate had m.p. 68°. The analytical data agree with 2,5-dimethyl-3-acetoxy-2,3-dihydrobenzofuran (XXI).

Oxidation of Allyl and Propenyl Derivatives of Guaiacol by Acetyl Hydroperoxide.

Preparation of the oxide of allyl guaiacol ether, 1-(o-methoxyphenoxy)-oxido-2,3-propane (IV). Allyl guaiacol ether was prepared in 78.4% yield from allyl bromide and guaiacol [2,8-11]. B.p. 114.5° (8 mm), n_D^{20} 1.5338, d_4^{20} 1.1630, MR_D 48.33; calculated 47.60.

15.1 g of acetyl hydroperoxide 69.2% was added to 30 g of allyl guaiacol ether in 60 ml of anhydrous ether. The reaction proceeded smoothly, without heat evolution. At the end of the oxidation the solution became a bright orange color. After 12 days the reaction products were treated in the usual way. The distillation yielded 9.3 g of the unchanged allyl guaiacol ether and 9.1 g of the oxide of this ether. B.p. 138° (5 mm), n_D^{20} 1.5390, d_4^{20} 1.1630, MR_D 48.52, calculated 47.64.

Found %: C 66.55; H 6.50; M 179.9, 179.70.
$C_{10}H_{12}O_3$. Calculated%: C 66.66; H 6.66; M 180.

Preparation of the oxide of o-allylguaiacol (o-eugenol), 2-methoxy-6-(2,3-oxidopropyl)-phenol (VII). o-Allyl guaiacol was prepared in 80% yield by boiling allyl guaicol ether 3.5 hours at 240° in an atmosphere of carbon dioxide [8-12]. B.p. 152° (26 mm), n_D^{20} 1.5395, d_4^{20} 1.0671, MR_D 48.18; calculated 47.48.

40 g of o-eugenol in 80 ml of anhydrous ether was oxidized by 20.1 g of acetyl hydroperoxide (92%). The reaction proceeded with slight heat evolution. Toward the end of the addition of the hydroperoxide the solution turned an orange-red color. After 3 days the oxidation products were treated by the usual method; 2-fold vacuum distillation yielded 12 g of an orange colored liquid. B.p. 153-158° (5 mm), n_D^{20} 1.5545, d_4^{20} 1.2090, MR_D 47.76; calculated 47.52.

Found%: C 66.76; H 6.72; OH 8.62; M 193.6, 195.2.
$C_{10}H_{12}O_3$. Calculated%: C 66.66; H 6.66; OH 9.94; M 180.

Preparation of 1-methoxy-2-acetoxy-3-(2,3-oxidopropyl)-benzene (XI). 3.5 g of o-eugenol oxide (VII) in 10 ml of acetic anhydride was boiled 2.5 hours in a flask under a reflux condenser. After removal of acetic anhydride the substance was distilled three times under vacuum. The yield was 1.0 g of a thick yellowish liquid. B.p. 163-164° (5 mm), n_D^{20} 1.5293, d_4^{20} 1.1980, MR_D 57.18; calculated 57.08.

Found%: C 64.57; H 6.50; M 221.4.
$C_{12}H_{14}O_4$. Calculated%: C 64.86; H 6.30; M 222.

Preparation of o-isoeugenol oxide (o-propenylguaiacol), 2-methoxy-6-(1,2-oxidopropyl)-phenol (IX). o-Isoeugenol was prepared from o-eugenol by heating the latter with moist caustic potash [2, 9, 11, 12]; m.p. 72° (from hexane). 30 g of o-isoeugenol in 115 ml of anhydrous ether was oxidized by 15 g of acetyl hydroperoxide (97%). The reaction was accompanied by much heat evolution. The temperature was maintained at 20-25° by cooling the reaction mixture with cold water. After 2 days the oxidation products were treated in the usual way. Vacuum distillation gave 21 g substance, b.p. 110-145° (4 mm) which crystallized. Recrystallization from benzene yielded 12 12 g with m.p. 88-89°. Found %: C 66.80; H 6.75. M 176.5, $C_{10}H_{12}O_3$. Calculated %: C 66.66; H 6.66. M 180.

Preparation of 1-methoxy-2-acetoxy-3-(2,3-oxidopropyl)-benzene (XXIII). 3 g of o-isoeugenol oxide (IX) in 10 ml of acetic anhydride was gradually heated. The crystals dissolved and the mixture turned a bright orange color. After a few minutes the color became pale yellow and remained until the boiling of the mixture, which was continued 1 hour, ceased. The acetic anhydride was distilled off under vacuum. 2-fold vacuum distillation of the residue yielded 0.5 g of viscous, slightly greenish liquid. B.p. 158° (5 mm), n_D^{20} 1.5230, d_4^{20} 1.1565, MR_D 58.63; calculated 57.08.

Found %: C 64.39; H 6.75; M 209.5, 212.7.
$C_{12}H_{14}O_4$. Calculated%: C 64.84; H 6.30; M 222.

No active hydrogen present.

SUMMARY

1. Acetyl hydroperoxide was used to oxidize p-cresol and guaiacol allyl ethers, o-allyl-m-cresol, o-allyl-p--cresol, o-methoxy-o-allylphenol (o-eugenol), o-propenylphenol -m-cresol, and o-methoxy-o-propenylphenol (o--isoeugenol), and the following oxides were obtained: 1-(p-tolyloxy)-oxido-2,3-propane, 1-(o-methoxy-phenoxy)--oxido 2,3-propane, 3-methyl-6-(2,3-oxidopropyl)phenol, 2-methoxy-6-(2,3-oxidopropyl)-phenol, 3-methyl-6--(1 2-oxidorpopyl)-phenol, and 2-methoxy-6-(1,2-oxidopropyl)-phenol.

2. The oxidation of o-propenyl-p-cresol yielded 2,5-dimethylbenzofuran, 1-acetoxy-1-(3-methyl-6-hydroxy-phenyl)-propanol-2, and 2,5-dimethyl-3-acetoxy-2,3-dihydrobenzofuran. The oxide was not isolated.

3. The oxides of o-allyl-p-cresol, o-methoxy-o-allylphenol (o-eugenol), and o-methoxy-o-propenylphenol (o--isoeugenol), when heated with acetic anhydride, are acetylated at the phenolic hydroxyl to form oxidoacetates.

4. The oxide of o-propenyl-m-cresol when stored over sulfuric acid in a desiccator, and the oxide of o-iso-eugenol when heated with potassium bisulfate, yield coumarone derivatives.

5. In the conversion of the oxides of phenol propenyl derivatives into coumarone derivatives, the furan ring is most probably formed with participation of oxygen from the phenolic hydroxyl group.

6. It was established that in the rearrangement of m-cresol allyl ether the allyl group is displaced into the para-position relative to the methyl group.

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* T.p. = C.B. Translation pagination.

HYDRATION OF DECYNE-5-DIOL-4,7 BY MEANS OF THE KUCHEROV REACTION

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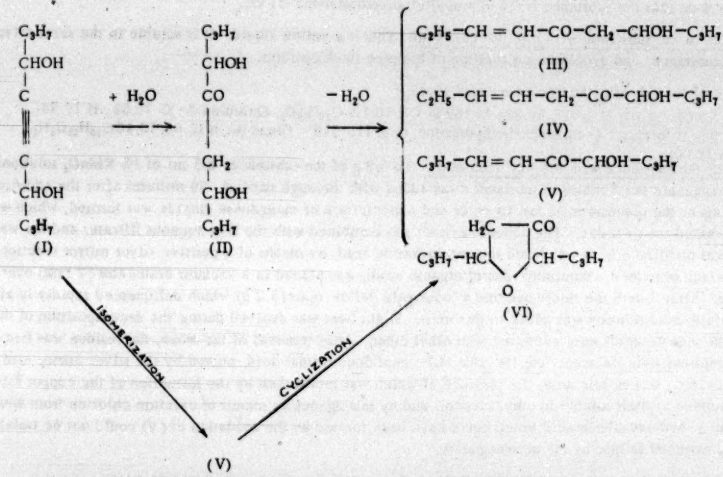
Many acetylenic alcohols have been hydrated in the conditions of the M. G. Kucherov reaction, the primary products of which are keto alcohols [1-3]. The hydration of acetylenic alcohols is often followed by dehydration with the formation of unsaturated ketones [4,5]. γ-Glycols of the acetylene series yield ketones of the tetrahydrofuran series, which are the final reaction products, while the initial hydration products cannot be isolated [6].

For verification of these results we synthesized, from butyraldehyde and acetylenedimagnesium dibromide, the secondary acetylenic glycol, decyne-5-diol-4,7 (I), and hydrated it with the aid of M. G. Kucherov's method. The reaction may result in the formation of a keto glycol, the first hydration product (II), and also of the dehydration products – unsaturated acyclic hydroxyketones (III,IV,V) and a ketone of the tetrahydrofuran series (VI).



Investigation of the reaction products showed that they consist of two compounds, an unsaturated keto alcohol, decene-4-ol-7-one-6 (V), and a ketone, 2,5-dipropyltetrahydrofuranone-3 (VI).

The structure of the keto alcohol (V) was proved by its oxidation by 1% potassium permaganate solution, decoloration of a chloroform solution of bromine, and the formation of the 2,4-dinitrophenylhydrazone. The ketone (VI) had saturated properties, did not contain a hydroxyl group, and formed a semicarbazone.

The formation of these compounds may be represented as follows: the action of mercuric sulfate solution on decyne-5-diol-4,7 (I) results in the addition of water with the formation of the keto glycol (II), which was not isolated. The keto glycol may be dehydrated in two different ways, which can result in the formation of the keto alcohol (V) or the ketone (VI).

If it is taken into account that the hydroxyl groups which are in the α-position relative to the triple bond in acetylenic alcohols are very mobile [7,8], then the possibility is not excluded that the keto alcohol (V) might be formed directly from the acetylenic glycol (I) by isomerization, and the ketone (VI) from the keto alcohol (V) by cyclization [9,10].

EXPERIMENTAL

Hydration of decyne-5-diol-4,7. To 70 g of glycol (b.p. 154-156° at 12 mm, d_{20}^{20} 0.9514, n_D^{20} 1.4630, MR_D 49.26; calculated 49.43), 288 g of aqueous mercuric sulfate solution (5 g HgO, 25 g concentrated H_2SO_4, and 170 ml H_2O) was added. The mixture was heated 3 hours on the water bath at 60-70°, cooled, and extracted with ether; the ether extract was washed with 10 % soda solution and water, and dried with sodium sulfate. The ether was distilled off, and the residue yielded two substances after 3 distillations, 1) b.p. 65-66° (0.5 mm), 20.4 g; 2) b.p. 83° (0.5 mm), 12 g.

Investigation of the substance with b.p. 65-66° (0.5 mm). This is a mobile slightly yellowish liquid. It is soluble in ethyl alcohol, ethyl ether, chloroform, and benzene, and is insoluble in water; it does not decolorize a solution of bromine in chloroform at room temperature and does not react with dimethylmagnesium iodide:

d_4^{20} 0.9324 n_D^{20} 1.4398, MR_D 48.07; calculated 47.83.

Found %: C 70.75, 70.50; H 10.95, 10.62. M 170.3. $C_{10}H_{18}O_2$. Calculated %: C 70.53; H 10.66. M. 170.1.

With semicarbazide it forms a semicarbazone, m.p. 103-104°, and with 2,4-dinitrophenylhydrazine, it forms the corresponding hydrazone, m.p. 94-95°.

For the 2,4-dinitrophenylhydrazone, found %: N 15.94, 16.10. $C_{16}H_{22}O_5N_4$. Calculated %: N 16.00.

The results show that the substance is 2,5-dipropyltetrahydrofuranone-3 (VI).

Investigation of the substance with b.p. 83° (0.5 mm). This is a yellow liquid. It is soluble in the same solvents as the preceding substance, and decolorizes a solution of bromine in chloroform.

d_4^{20} 0.9308, n_D^{20} 1.4603, MR_D 50.07; calculated 49.45.

Found %: C 70.06, 70.13; H 10.73, 10.83; M 169.9; OH 10.12. $C_{10}H_{18}O_2$. Calculed %: C 70.53; H 10.66. M 170.14; OH 9.99. It forms a 2,4-dinitrophenylhydrazone, m.p. 116-118°. Found %: N 16.08, 16.15 $C_{16}H_{22}O_5N_4$. Calculated %: N 16.00.

Oxidation of the substance with b.p. 83° (0.5 mm). To 3.2 g of the substance, 495 ml of 1% $KMnO_4$ solution (5 moles of permanganate per 3 moles of substance) was added with thorough stirring. 20 minutes after the addition of the oxidizing agent the reaction mass lost its color and a precipitate of manganese dioxide was formed, which was filtered off and washed the next day. The aqueous extract was combined with the first aqueous filtrate, and the water from the whole was distilled off; it was found to contain formic acid, by means of a positive silver mirror reaction. The oily liquid which remained, containing salts of organic acids, was placed in a vacuum desiccator (2 mm) over calcium chloride. After 7 days the liquid became a loose pale yellow mass (3.2 g) which deliquesced rapidly in air. 30 ml of 10% sulfuric acid solution was added to this mass. Slight heat was evolved during the decomposition of the organic salts. The organic acids were extracted with ethyl ether. After removal of the ether, the residue was fractionated. Two fractions were isolated; the 1st, 101-110°, contained formic acid, proved by the silver mirror reaction; the 2nd, 160-169°, was butyric acid, the presence of which was established by the formation of the copper salt in the form of rhombic crystals soluble in ethyl alcohol, and by salting-out by means of calcium chloride from aqueous solution. The α-hydroxyvaleric acid which could have been formed by the oxidation of (V) could not be isolated. It was apparently oxidized further by the permanganate.

Thus, the substance in question may be regarded as a keto alcohol – decyne-4-ol-7-one-6 (V).

SUMMARY

The action of mercuric sulfate solution on a secondary acetylenic glycol, decyne-5-diol-4,7, yielded an unsaturated keto alcohol, decene-4-ol-7-one-6, and a cyclic ketone, 2,5-dipropyltetrahydrofuranone-3.

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SYNTHESIS AND HYDROGENATION OF 6-METHYLHEPTEN-1-YNE-4-DIOL-3,6

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We established earlier that α,β-unsaturated ketones react at low temperatures with unsaturated organomagnesium compounds with the formation of enyne and dienyne carbinols [1].

The action of unsaturated hydroxymagnesium organic compounds on unsaturated aldehydes has been studied very little [2]; our aims therefore were to study the action of acrolein on dimethylacetylenyl carbinol magnesium bromide, to prepare the secondary-tertiary enyne glycol, and to investigate its hydrogenation in the presence of catalysts.

It was found that at −7° the reaction of glycol formation proceeds normally, to yield 6-methylhepten-1--yne-4-diol-3,6 (I):

$$(CH_3)_2COH-C\equiv C-CHOH-CH=CH_2 \rightarrow$$
(I)

$$\rightarrow (CH_3)_2COH-CH_2-CH_2-CHOH-CH_2-CH_3.$$
(II)

In the presence of platinum black this glycol adds on 6 hydrogen atoms, and the reaction rate gradually diminishes. There is no break in the hydrogenation rate after the addition of two or four hydrogen atoms. The hydrogenation product is a mobile oil which does not decolorize bromine water. Analysis confirms that the substance is 2-methylheptanediol-2,5 (II).

In the presence of colloidal palladium the enyne glycol (I) adds on the first 4 hydrogen atoms much more vigorously. The last 2 hydrogen atoms are added more slowly, and the same saturated glycol is formed.

EXPERIMENTAL

33 g of dimethylacetylenyl carbinol in 33 ml of anhydrous ether was added dropwise to ethylmagnesium bromide prepared by the usual method (from 24.2 g of magnesium and 93 g of ethyl bromide). 40 g of acrolein in 40 ml of anhydrous ether was added to the organomagnesium compound (at −7 to −8°). The complex was decomposed by 15% ammonium sulfate solution and then by 10% sulfuric acid. After removal of the ether layer, the aqueous layer was extracted with ether. After drying with Na_2SO_4 and removal of ether, 18 g of a viscous yellowish oil was obtained.

B.p. 106-107° (3-4 mm), d_{15}^{15} 0.9988, n_D^{15} 1.4772, MR_D 39.59; calculated 41.48.

Found %: C 68.02; H 8.55; OH 24.18. M 141. $C_8H_{10}(OH)_2$. Calculated %: C 68.50; H 8.50; OH 24.28. M 140.

Hydrogenation of 6-methylhepten-1-yne-4-diol-3,6. 1.40 g of the glycol, 50 ml of C_2H_5OH, and 0.75 g of platinum black was taken; 18°, 733 mm; $3H_2$ 757 ml. The amounts of hydrogen (in ml) added each 6 minutes were: 231, 149, 95, 84, 63, 51, 47, 33, 15, 6, 1. The total hydrogen added in 54 minutes was 768 ml.

The analytical data of the hydrogenation product were:

B.p. 63-67° (3-4 mm), d_{20}^{20} 0.8395, n_D^{20} 1.4285, MR_D 44.05; calculated 42.19.

Found %: C 65.74; H 12.85; OH 23.23. M 142.8. $C_8H_{16}(OH)_2$. Calculated %: C 65.75; H 12.34; OH 23.28. M 146.

1.4 g of the glycol, 50 ml of C_2H_5OH and 3 mg of palladium, at 24°, and 727 mm; $3H_2$, 768 ml, was taken.

The amounts of hydrogen added each 3 minutes were (in ml): 217, 208, 175, 58, 22, 12 etc. The total hydrogen added in 33 minutes was 770 ml.

The same substance was obtained after distillation as in the presence of platinum.

SUMMARY

It was shown that magnesiumbromodimethylacetylenyl carbinol bromide reacts with acrolein and forms a glycol, 6-methylhepten-1-yne-4-diol-3,6, which is described for the first time.

The hydrogenation of the glycol in the presence of platinum black and of colloidal palladium was studied, and 2-methylheptanediol-2,5 was isolated.

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A NEW METHOD FOR THE PREPARATION OF HYDROXY ACIDS

PREPARATION OF 10-HYDROXYUNDECANOIC AND 14-HYDROXYBEHENIC ACIDS

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It is known that the methods for the preparation of hydroxy acids which have been developed by a number of workers do not always give good results owing to side reactions. This applies to the main methods for the preparation of hydroxy acids – replacement of halogen by hydroxyl in halogenated acids, and hydration of unsaturated acids.

In 1939 we published our paper [1] on the catalytic hydrogenation of the oxides of unsaturated acids. It was shown that the ethyl ester of oleic acid oxide is hydrogenated in the presence of palladium black to form the ethyl ester of 10-hydroxystearic acid; the formation of the ethyl ester of 9-hydroxystearic acid was not observed. Later, one of the present authors established together with T. A. Starostina [2] that this reaction may be used for the synthesis of hydroxy acid triglycerides. In the present communication it is shown that this reaction is a general one and may be used as a method for the preparation of hydroxy acids.

The starting substances were the ethyl esters of undecylenic [3] and erucic acid oxides. The ethyl ester of undecylenic acid oxide was hydrogenated in the presence of palladium catalyst. As the result of the hydrogenation the ethyl ester of hydroxyundecanoic acid, not described previously was prepared. The properties of the hydroxyundecanoic acid prepared by saponification of the ester agreed with the properties of 10-hydroxyundecanoic acid [4-7]. The hydrogenation proceeded quantitatively without formation of side products such as the structural isomer, the ethyl ester of 11-hydroxyindecanoic acid.

The ethyl ester of the oxide of erucic acid was hydrogenated in a manner analogous to that used for hydrogenation of the ethyl ester of oleic acid oxide. Hydrogenation in ethyl alcohol was not accompanied by side reactions, and yielded a homogeneous product, the ethyl ester of hydroxybehenic acid. When the hydrogenation was carried out in acetic acid medium, the hydrogenation continued after the addition of 1 mole of hydrogen, and led to the formation of side products. The ethyl ester of hydroxybehenic acid which we obtained had a much higher melting point (60.5-61.0°) than that given in the literature (46.6 - 47.8, 49.5°). It seems likely that Grun and Janko [9] prepared the ethyl ester (by the esterification of hydroxybehenic acid in the presence of β-naphthalenesulfonic acid) in a form contaminated by dehydration products. Grace and Zuckerman [10], who repeated the work of the above authors, with some modifications, used nonhomogeneous hydroxybehenic acid as their starting material (m.p. 80°). In addition, the ethyl ester which they synthesized was undoubtedly partially dehydrated during vacuum distillation. From the ethyl ester of hydroxybehenic acid we isolated hydroxybehenic acid with m.p. 89.5-90°, which is characteristic for 14-hydroxybehenic acid and differs from the melting point of 13-hydroxybehenic acid (87-87.5°). The structure of the hydroxybehenic acid synthesized was further confirmed by the preparation of the ethyl ester of ketobehenic acid, ketobehenic acid, and its oxime. All these compounds had the properties of 14-ketobehenic acid and its derivatives (Table 1).

Without a doubt, the hydrogenation reaction proceeded only in one direction, and one of the possible structural isomers was formed. The hydroxyl group, as in the hydrogenation of the ethyl ester of oleic acid oxide, took a position furthest from the carboxyl group.

EXPERIMENTAL

Preparation of the ethyl ester of undecylenic acid. The starting material was undecylenic acid isolated from the technical product, b.p. 159-160° (11 mm), m.p. 24.0-24.5°, neutralization equivalent 184.5. The ethyl ester was prepared from the undecylenic acid and anhydrous ethyl alcohol in the presence of concentrated sulfuric acid. B. p. 129-131° (10 mm), iodine number 118.9, saponification number 264.4.

TABLE 1

Name of Compound	Melting point	
	substance studied	according to the literature
14-Ketobehenic acid ethyl ester	53.7–54.0°	54° [12, 13]
14-Ketobehenic acid oxime	49–51	44–45 [12], 49–51 [13]
14-Ketobehenic acid	84.0–84.5	83 [12], 83–84 [13, 17] 84.5 [14], 82–83 [15], 85 [11]

TABLE 2

Time (hours)	H_2 Absorbed (in ml) •	Time (hours)	H_2 Absorbed (in ml) •
0.5	81	3.5	241
1.0	139	4.0	244
1.5	182	4.5	246
2.0	211	5.0	248
2.5	227	5.5	250
3.0	236	6.0	252

TABLE 3

Time (hours)	H_2 absorbed (in ml)	Time (hours)	H_2 absorbed (in ml)
0.5	47	3.5	202
1.0	87	4.0	215
1.5	119	4.5	225
2.0	146	5.0	233
2.5	169	5.5	239
3.0	186	6.0	243
		6.5	246

• The pressure of water vapor at the given temperature was taken into account in calculations of the volume of hydrogen for hydrogenation.

Preparation of the ethyl ester of undecylenic acid oxide. Acetyl hydroperoxide was used to oxidize the ethyl ester of undecylenic acid. A solution of 74 ml of acetyl hydroperoxide (containing 0.1288 g of active hydrogen per 1 ml) in 200 ml of anhydrous ether was added to a solution of the ethyl ester of undecylenic acid in 150 ml of anhydrous ether cooled in ice-cold water. The excess of active oxygen was 10%. The reaction proceeded with slight evolution of heat; therefore the solution was first cooled 3 hours and then left to stand at room temperature. The oxidation was completed after 16 days. At the end of the oxidation the ether solution was washed first with water, then with 5% soda solution, then again with water to a neutral reaction. After the mixture had been dried and the ether removed, the side products were separated by means of 2-fold vacuum distillation. The main fraction (30.1 g) had b.p. 121-123° (0.1 mm).

d_4^{20} 0.9523, n_D^{20} 1.4429, MR_D 63.55; calculated 63.33

Found %: C 68.50, 68.19; H 10.86, 10.81; saponification number 245.7, 246.9. $C_{13}H_{24}O_3$. Calculated %: C 68.38; H 10.60; saponification number 245.7.

Hydrogenation of the ethyl ester of undecylenic acid oxide. The hydrogenation was carried out in bulbs of 150 ml capacity in anhydrous alcohol solution in the presence of palladium black prepared by Willstätter's method and precreated with anhydrous ether as recommended by K. A. Taipale.

The amounts taken were 2.283 g of ethyl ester of undecylenic acid oxide, 30 ml of anhydrous alcohol, and 0.36 g of palladium black. The pressure was 747.4 mm, and the temperature 20°. The theoretical amount of H_2 required is 250.3 ml.

The course of the hydrogenation is shown in Table 2.

The hydrogenation ceased after the addition of 1 mole of hydrogen.

Isolation of the hydrogenation products. Alcohol was removed under vacuum from the alcohol solution after removal of the catalyst. The hydrogenation product was a colorless mobile liquid. For ease of distillation, the hydrogenation products from several experiments were combined. 20.76 g of the ethyl ester of undecylenic acid oxide yielded 20.48 g of the hydrogenated product, distillation of which under vacuum (0.08 mm) gave two

fractions: 1st, 127-129°, 2.72 g; 2nd, 129-131°, 16.45 g.

Investigation of the 2nd fraction $d_4^{19.8}$ 0.9394, $n_D^{19.8}$ 1.4456, MR_D 65.33; calculated 65.41. Found %: C 67.55, 67.63; H 11.42, 11.48; active H number 0.96, 1.08; saponification number 243.3. $C_{13}H_{26}O_3$. Calculated %: C 67.78; H 11.38, active H number 1, saponification number 243.6.

Investigation of the 1st fraction; $d_4^{19.8}$ 0.9390, $n_D^{19.8}$ 1.4441, MR_D 65.17; calculated 65.41. Found: active H number 0.93, 0.98; saponification number 244.4. $C_{13}H_{26}O_3$. Calculated: active H number 1, saponification 243.3.

Preparation of hydroxyundecanoic acid from the ethyl ester. 2.66 g of the ethyl ester of hydroxyundecanoic acid was saponified with 75 ml of 0.5 N alcoholic KOH solution. After neutralization of the solution with dilute sulfuric acid and removal of the alcohol, the hydroxy acid (2.06 g) was isolated by acidification followed by ether extraction. After recrystallization from ligroine and from ligroine-benzene mixture, the hydroxy acid had m.p. 49.0-49.5°. No melting point depression was given by a sample mixed with synthesized 10-hydroxyundecanoic acid••.

Found %: C 65.27, 65.56; H 11.10, 11.15; neutraliz. equiv. 202.9. $C_{11}H_{22}O_3$. Calculated %: C 65.31; H 10.96; neutraliz. equiv. 202.3. The same hydroxy acid with m.p. 49.0-49.5° was isolated from the 1st fraction.

Preparation of the ethyl ether of erucic acid. The erucic acid used for the preparation of the ester was isolated from rapeseed oil by the method of Doree and Pepper [8]; m.p. 33.4-33.8°, iodine number 71.76. Esterification of the acid was carried out under the conditions cited for undecylenic acid. The ethyl ester of erucic acid had b.p. 193-194° (0.14 mm), iodine number 65.67, saponification number 153.1.

Oxidation of the ethyl ester of erucic acid by acetyl hydroperoxide. The acetyl hydroperoxide was prepared from boroacetic anhydride. An ether solution of acetyl hydroperoxide (87.4 ml in 400 ml of ether) was added with cooling to a solution of 188.4 g of the ethyl ether of erucic acid dissolved in 90 ml of anhydrous ether. Excess active oxygen (37%) was taken. The reaction was completed in 3 days. The conditions for isolation of the oxide were the same as in the synthesis of the oxide of the ethyl ester of undecylenic acid. The properties of the ethyl ester of erucic acid oxide are: b.p. 207-208° (0.18 mm); m.p. 29.0-29.5°; iodine number 0.

Found %: C 75.34, 75.28; H 12.35, 12.21; saponification number 146. $C_{24}H_{46}O_3$. Calculated %: C 75.34; H 12.12; saponification number 146.6.

Hydrogenation of the ethyl ester of erucic acid oxide. The hydrogenation was performed in the conditions described above. We describe one of the hydrogenation experiments.

Weight taken 3.826 g, with 30 ml of anhydrous ethyl alcohol and 0.40 g of palladium black. Pressure 756.4 mm, temperature 16.8°. The theoretical amount of H_2 required is 243.5 mm (Table 3)•.

Isolation and investigation of the hydrogenation products. 11.48 g of the ethyl ester of erucic acid oxide yielded 11.21 g of a substance with m.p. 58.3-59.0°. After recrystallization from ethyl acetate and then from alcohol, m.p. 60.6-61.0°. Found %: C 74.86, 75.14; H 12.75, 12.69; active H number 1.02, 1.04; saponification number 145.7, 146.3. $C_{24}H_{48}O_3$. Calculated %: C 74.94; H 12.58; active H number 1; saponification number 145.9. Saponification of the ethyl ester of hydroxybehenic acid yielded the hydroxy acid, which after recrystallization from alcohol had m.p. 89.5-90.0°. Found %: C 74.19, 74.26; H 12.64, 12.58, neutraliz. equiv. 357.2. $C_{22}H_{44}O_3$. Calculed %: C 74.10, H 12.44; neutraliz. equiv. 356.6.

Oxidation of the ethyl ester of hydroxybehenic acid by chromic anhydride in glacial acetic acid. To 20 g of the ethyl ester of hydroxybehenic acid in 200 ml of glacial acetic acid, a solution of 3.5 g of chromic anhydride in 250 ml of glacial acetic acid was added gradually during 1 hour with shaking. The deep violet reaction mixture turned green when heated 15 minutes on the water bath the next day. When the cooled solution was diluted with water, a fine white precipitate was formed, which was filtered off and washed with water. The total yield was 19.5 g. After 2-fold crystallization from alcohol the substance had m.p. 53.7-54°.

• If the hydrogenation is performed in glacial acetic acid, it proceeds more rapidly and does not stop after the absorption of 1 mole of hydrogen. The hydrogenation product, in addition to the ethyl ester of hydroxybehenic acid, also contained as an impurity (12%) a substance with m.p. 31.5-36.7°. This substance had a small active H value, 0.30.

•• 10-Hydroxyundecanoic acid was synthesized from bromodecanoic acid by the reaction with potassium acetate in glacial acetic acid solution followed by saponification of the acetylated product [4].

Found %: C 75.31, 75.52; H 12.38, 12.16; saponification number 147.2, 146.4. Does not contain hydroxyl groups. $C_{24}H_{46}O_3$. Calculated %: C 75.34; H 12.12; saponification number 146.6.

Preparation of ketobehenic acid. Saponification of 6.78 g of the ethyl ester followed by acidification yielded 6.05 g of ketobehenic acid, m.p. 83.5-84.0°. After recrystallization from alcohol, m.p. 84.0-84.5°.

Found %: C 74.58, 74.78; H 12.09, 12.21; active H number 1.03; neutraliz. equiv. 355.3. $C_{22}H_{42}O_3$. Calculated %: C 74.52; H 11.94; active H number 1; neutraliz. equiv. 354.6.

Preparation of ketobehenic acid oxime. The oxime was prepared by the method described by Auwers [16], as follows. 3.5 g of ketobehenic acid was dissolved in alcoholic caustic soda solution (2.8 g of NaOH in 70 ml of alcohol); 1.4 g of hydroxylamine hydrochloride was then added to the solution. The reaction mixture was heated 2 hours on the boiling water bath. The next day the residue, after removal of the alcohol, was dissolved in water. The alkali was neutralized by a small excess of hydrochloric acid. The oxime after 2-fold crystallization from alcohol had m.p. 49-51°.

Found %: N 3.81, 4.04. $C_{22}H_{43}O_3N$. Calculated %: N 3.79.

SUMMARY

The ethyl ester of undecylenic acid oxide is readily hydrogenated in the presence of palladium black with a quantitative yield of the ethyl ester of 10-hydroxyundecanoic acid, not previously described. The ethyl ester of erucic acid oxide, which was prepared for the first time, when hydrogenated in the presence of Pd catalyst forms the ethyl ester of 14-hydroxybehenic acid, with m.p. 60.5-61.0, a value which differs greatly from that given in the literature.

If ring opening occurs, as in the case of the ethyl ester of oleic acid oxide, the hydroxyl takes up a position further removed from the carboxyl group.

A general method for the preparation of hydroxy acids is described, based on hydrogenation of esters of unsaturated acid oxides followed by saponification.

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PREPARATION OF ALKYLANILINES

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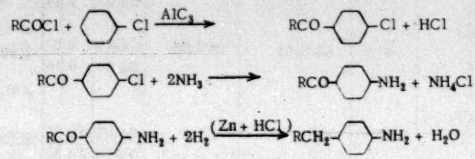
It is known that aniline homologs may be obtained by two principal methods – the reduction of the corresponding nitro compounds [1] prepared by nitration of alkylbenzenes, or by C-alkylation of aniline by alcohols in the presence of hydrogen chloride and zinc chloride [2]. In addition, alkylanilines are obtained by the reduction of alkyl-4-aminophenyl ketones by various reducing agents [3].

For the preparation of aniline homologs having a normal aliphatic chain of 2 or more carbon atoms in the para position to the amino group, we made use of reduction by means of amalgamated zinc and hydrochloric acid. It is reported [4] that when 4-aminoacetophenone is reduced by this method in an aqueous medium the yield of 4-ethylaniline does not exceed 19.5%. The reduction of such ketones with more than 3 carbon atoms in the aliphatic chain has not previously been carried out.

The whole synthesis was performed according to the following scheme:



(R = CH_3, n-C_5H_{11}, n-C_9H_{19}, n-$C_{11}H_{23}$, n-$C_{13}H_{27}$, n-$C_{17}H_{35}$).

In order to establish the absence of isomerization of the carbon chain during the condensation process, and to determine the point of entry of the acyl group, the oxime of n-undecyl 4-chlorophenyl ketone was prepared, which, by the Beckmann rearrangement, was converted into lauric acid 4-chloroanilide. The product proved identical with the anilide prepared from 4-chloroaniline and lauryl chloride.

The method was used to prepare ethylaniline, n-hexylaniline, n-octylaniline, n-dodecylaniline, and n-octadecylaniline.

It is interesting to note that the yields in the reduction stage increase with increasing numbers of carbon atoms in the aliphatic chain of alkyl 4-aminophenyl ketones (from 28.1 to 77.8%).

EXPERIMENTAL •

Preparation of the ketones. A solution of 0.2-0.5 mole of the acid chloride in 200-300 ml of chlorobenzene was placed in a three-necked round-bottomed flask fitted with a reflux condenser, stirrer, and thermometer, and 0.25-0.6 mole of anhydrous aluminum chloride was added. The mixture was stirred 1 hour without heating and 1 hour at 100°, then poured into 1-2 liters of cold water and separated. In the case of compounds with more than 10 carbon atoms in the side chain, the excess chlorobenzene was distilled in steam, while the residue was filtered and recrystallized from alcohol. In the other cases, the chlorobenzene was distilled off under atmospheric pressure, while the residue was distilled under vacuum. The 2,4-dinitrophenylhydrazones were prepared by the usual method [5].

The results of the experiments are shown in Table 1.

The oxime of n-undecyl 4-chlorophenyl ketone. A solution of 2.95 g of n-undecyl 4-chlorophenyl ketone and 1 g of hydroxylamine hydrochloride in 30 ml of alcohol was neutralized with 20% caustic soda, then sealed in an ampoule and heated 12 hours on the boiling water bath. The cooled reaction mass was filtered into 100 ml of 2%

• E. N. Karpova participated in the preparation of compounds with 18 carbon atoms in the side chain.

hydrochloric acid. The oxime formed had m.p. 37.5-38° (from methanol).

Found %: N 4.89, 4.78. $C_{18}H_{28}ONCl$. Calculated %: N 4.52.

TABLE 1

Serial No.	Name and formula	Yield (%)	Melting point	Boiling point, at pressure (mm)	Analytic data (%) Found C	Found H	Calc. C	Calc. H	Melting point of 2,4-dinitrophenylhydrazone
1	4-Chloroacetophenone $CH_3COC_6H_4Cl$	64.0	18.0° [7]	100° (8)	–	–	–	–	231-232° [6]
2	n-Amyl 4-chlorophenyl ketone $C_5H_{11}COC_6H_4Cl$	77.0	50-50.5	136 (3)	68.52, 68.62	7.17 7.30	68.50	7.32	159-159.5
3	n-Heptyl 4-chlorophenyl ketone $C_7H_{15}COC_6H_4Cl$	76.3	57.5	192.5 (15)	70.61 70.75	8.08 8.16	70.42	8.02	146.5
4	n-Undecyl 4-chlorophenyl ketone $C_{11}H_{23}COC_6H_4Cl$	99.2	57.5-58	215 (15)	73.16 73.23	9.35 9.34	73.31	9 23	105 7
5	n-Tridecyl 4-chlorophenyl ketone $C_{13}H_{27}COC_6H_4Cl$	97.5	63.5-64	230 (5)	74.47 74.60	9.87 9.76	74.39	9.68	108-108.5
6	n-Heptadecyl 4--chlorophenyl ketone $C_{17}H_{35}COC_6H_4Cl$	97.0	73-73.5	–	75.82 75.93	10.27 10.38	76.05	10.37	101-101.2

TABLE 2

Serial No.	Name and formula	Yield (%)	Melting point	Analytical data for nitrogen (%) Found	Calculated	Melting point of acetyl derivative
1	4-Aminoacetophenone $CH_3COC_6H_4NH_2$	91.8	106-106.5° [9]	–	–	167° [9]
2	n-Amyl 4-aminophenyl ketone $C_5H_{11}COC_6H_4NH_2$	97.7	70-70.5	7.46,7.53	7.33	109-109.5
3	n-Heptyl 4- aminophenyl ketone $C_7H_{15}COC_6H_4NH_2$	92.5	105.7-106	6.59,6.47	6.39	129.8-130
4	n-Undecyl 4-aminophenyl ketone $C_{11}H_{23}COC_6H_4NH_2$	95.0	102.8-103	5.55,5.37	5.10	112.2
5	n-Heptadecyl 4--aminophenyl ketone $C_{17}H_{35}COC_6H_4NH_2$	97.0	106-106.4	4.40,4.33	3.90	116.5

Beckmann rearrangement [8] of the oxime. 10 g of phosphorus pentachloride was added to a solution of n-undecyl 4-chlorophenyl ketone oxime in dry ether, cooled in ice and stirred. After 10 minutes the ether layer was decanted.

washed with ice-cold water, and dried by potash. After removal of the ether, colorless needles were obtained (2 g), m.p. 89.4-89.5° (from benzene). A sample mixed with lauric acid 4-chloroanilide had m.p. 89.4-89.5°.

TABLE 3

Serial No.	Name and formula	Yield (%)	Melting point	Boiling point, at pressure (mm)	Melting point of acetyl derivative
1	p-Ethylaniline $C_2H_5C_6H_4NH_2$	28.1	216.5°	–	94–94.2° [1]
2	p-n-Hexylaniline $C_6H_{13}C_6H_4NH_2$	37.1	–	145–146° (15)	90.5–91 [10]
3	p-n-octylaniline $C_8H_{17}C_6H_4NH_2$	41.4	–	138–140 (5)	94.0 [10]
4	p-n-dodecylaniline $C_{12}H_{25}C_6H_4NH_2$	50.6	41.5–42° [10]	211–212 (10)	101.7–102 [10]
5	p-n-octadecylaniline $C_{18}H_{37}C_6H_4NH_2$	77.8	56.5–57	–	99–99.5

Replacement of chlorine by amino groups. A mixture of 0.08-0.1 mole of the alkyl 4-chlorophenyl ketone, 300 ml of aqueous ammonia, and 0.024-0.03 mole of cuprous chloride was placed in an autoclave of 0.5 liter capacity, and heated 6 hours with stirring at 250 to 270°. The reaction mixture was filtered, and the precipitate was washed with ammonia solution and water. The alkyl 4-aminophenyl ketone was dried in the air and recrystallized. The results of the experiments are shown in Table 2.

Preparation of alkyl anilines. 250 ml of 50% alcohol and 100 ml of concentrated hydrochloric acid was poured over 20-30 g of amalgamated zinc in a one-liter round-bottomed flask. 10-14 g of the alkyl 4-aminophenyl ketone to be reduced was added to the flask, and the mixture was boiled under a reflux condenser till all the zinc dissolved. 20 ml of concentrated hydrochloric acid was added to the flask every 2 hours. The mixture was then cooled and treated with caustic soda solution till alkaline to phenolphthalein paper. The alkyl aniline was extracted with benzene and distilled under vacuum. When the amines were solid, the reduction product was filtered off, converted into the free base by treatment with alkali solution, and recrystallized from methyl alcohol. The results of the experiments are shown in Table 3.

p-n-Octadecylaniline (4-amino-n-octadecylbenzene).

Found %: C 83.29; H 12.58, 12.48; N 4.14, 3.99. $C_{24}H_{43}N$. Calculated %: C 83.39; H 12.54; N 4.07.

4-Acetamino-n-octadecylbenzene.

Found %: N 3.69, 3.75. $C_{26}H_{45}ON$. Calculated %: N 3.61.

SUMMARY

1. It is shown that aniline homologs containing from 2 to 18 carbon atoms in the normal side chain can be prepared by the reduction of alkyl 4-aminophenyl ketones by amalgamated zinc and hydrochloric acid in aqueous alcohol medium.

2. The original alkyl 4-aminophenyl ketones are obtained in good yields by the replacement of chlorine by amino groups from the corresponding alkyl 4-chlorophenyl ketones and ammonia in the presence of cuprous chloride.

3. 22 new substances were prepared and described.

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A NEW METHOD FOR THE SYNTHESIS OF PHOSPHINIC AND THIOPHOSPHINIC ACID ESTERS

XXIV. THE ADDITION OF PHOSPHONOACETIC ACID NITRILE AND ITS HOMOLOGS TO ESTERS AND NITRILES OF UNSATURATED CARBOXYLIC ACIDS

A. N. Pudovik and N. M. Lebedeva

In continuation of our previous investigations on the addition of incompletely esterified phosphorous, thiophosphorous, and phosphinic acids, and also of phosphonoacetic ester and phosphonoacetone, to unsaturated compounds, which formed the basis of a new method for the synthesis of phosphinic and thiophosphinic acid esters [1], we have now studied the addition reactions between the nitriles and esters of α,β-unsaturated carboxylic acids and phosphonoacetic acid and its homologs. Phosphonoacetic acid nitrile was synthesized by A. E. Arbuzov's method from chloroacetonitrile and triethyl phosphite [2]. The chemical properties of this interesting compound, which may be regarded as the analog of cyanoacetic or phosphonoacetic ester, have practically not been studied at all. The presence of mobile hydrogen atoms in the methylene group, activated by the phosphonic and the strongly electronegative nitrile groups, should, in our opinion, confer on the nitrile of phosphonoacetic acid considerable activity in addition, alkylation, condensation, and similar reactions.

Experiments on the addition of esters of acrylic, methacrylic, crotonic, cinnamic, and maleic acids, and of acrylonitrile, fully confirmed our views. The reactions proceed in the presence of alkali metal alcoholates in milder conditions than those required for phosphonoacetic ester and phosphonoacetone. When methyl acrylate or methacrylate was used, the products of phosphonoacetic acid nitrile addition to one or two molecules of the ester were obtained:

$$CN-CH_2-P(=O)(OC_2H_5)_2 + CH_2=CR-COOCH_3 \xrightarrow{C_2H_5ONa}$$

$$\longrightarrow (C_2H_5O)_2P(=O)-CH(CN)CH_2CHRCOOCH_3 + (C_2H_5O)_2P(=O)C(CN)(CH_2CHRCOOCH_3)_2,$$

where R = H or CH_3.

The physical constants, yields, and analytical data for phosphorus, of the addition products of phosphonoacetic acid nitrile and methyl acrylate, methyl and butyl methacrylates, ethyl crotonate, maleate, and cinnamate, and acrylo- and vinylacetonitriles are shown in Table 1.

It was established by a series of experiments that alkylation of phosphonoacetic acid nitrile proceeds best if its potassium derivative is used and the reaction is carried out in ether-dioxane solution. The addition of dioxane to ether improves the solubility of the potassium derivative. If the sodium derivative of phosphonoacetic acid nitrile is used, the reaction is much slower because of its lower reactivity and solubility. It must be pointed out, however, that even if the potassium derivative is used, the alkyl derivatives are not always obtained in good yields. To bring some of the reactions about, fairly prolonged heating of the reaction mixtures is needed. The physical constants and the yields of the nitriles of α-diethylphosphonopropionic, -butyric, -valeric, -isovaleric, -caproic, and -vinylpropionic acids synthesized are shown in Table 2.

Some of the products were saponified in the presence of dilute hydrochloric acid. The phosphonocarboxylic acid so prepared were very viscous, thick liquids; the first signs of crystallization only appeared after several months.

The addition reactions between the nitriles of α-phosphonobutyric, α-phosphonovaleric, α-phosphonocaproic, and α-phosphonovinylpropionic acids and some esters of unsaturated carboxylic acids and some unsaturated nitriles

were studied. The reactions were carried out in the presence of alkali metal alcoholates. In the addition reactions with unsaturated acid esters a considerable induction period was observed, and more prolonged heating was required for the completion of these reactions than for the analogous reactions with phosphonoacetic acid nitrile. The physical constants, yields, and analytical data for phosphorus of the compounds synthesized are shown in Table 3.

Saponification of some of the substances listed in Table 3 yielded the corresponding alkyl phosphonoglutaric acids in the form of very viscous resinous products.

TABLE 1

Series No.	Formula	Boiling point at pressure (mm)	n_D^{20}	d_4^{20} *	MR_D Found	MR_D Calculated	Analysis for P (%) Found	Analysis for P (%) Calculated	Yield (%)
1	$(C_2H_5O)_2P(O)C(CH_2CH_2CN)_2$	— **	—	—	—	—	11.04, 10.81	10.95	82
2	$(C_2H_5O)_2P(O)CH(CN)CHCH_2CN$	170° (2)	1.4503	1.1129	58.93	58.78	12.51, 12.71	12.70	53.2
3	$(C_2H_5O)_2P(O)CH(CN)CH_2CH_2COOCH_3$	183—185 (1)	1.4470	1.1570	60.63	60.67	11.53, 11.85	11.78	50.3
4	$(C_2H_5O)_2P(O)C(CN)(CH_2CH_2COOCH_3)_2$	195 (1)	1.4565	—	—	—	8.98, 9.02	8.88	
5	$(C_2H_5O)_2P(O)CH(CN)CH(CH_3)COOCH_3$	165—167 (2)	1.4410	1.1175	65.45	65.29	10.97, 11.03	11.19	46.8
6	$(C_2H_5O)_2P(O)C(CN)[CH_2CH(CH_3)COOCH_3]_2$	177—180 (2)	1.4490	1.1242	89.97	90.03	8.73, 8.58	8.49	
7	$(C_2H_5O)_2P(O)CH(CN)CH(CH_3)COOC_2H_5$	199 (5)	1.4450	—	—	—	10.03, 9.81	10.03	56
8	$(C_2H_5O)_2P(O)CH(CN)CH(CH_3)CH_2COOC_2H_5$	158—160 (2)	1.4440	1.1058	69.92	69.90	10.55, 10.49	10.65	40.47
9	$(C_2H_5O)_2P(O)CH(CN)CH(COOC_2H_5)_2$	194 (3)	1.4480	—	—	—	8.67, 8.52	8.88	71.3
10	$(C_2H_5O)_2P(O)CH(CN)CH(C_6H_5)COOC_2H_5$	201—202 (1)	1.4815	1.1250	89.39	89.39	8.78	8.81	26.3

* The densities of some of the compounds synthesized were not determined because of their high viscosity.

** M.p. 75-76°.

TABLE 2

Serial No.	Formula	Boiling point at pressure (mm)	n_D^{20}	d_4^{20}	MR_D		Analysis for P (%)		Yield (%)
					Found	Calculated	Found	Calculated	
1	$(C_2H_5O)_2P(O)CH(CN)C_6H_5$	140—141° (11)	1.4310	1.0851	45.57	45.16	15.97, 16.21	16.23	87.5
2	$(C_2H_5O)_2P(O)CH(CN)C_6H_4$	119 (3)	1.4328	1.076	49.49	49.78	15.10, 15.32	15.12	58.0
3	$(C_2H_5O)_2P(O)CH(CN)CH_2CH_2CH_3$	151 (10)	1.4365	1.0578	54.18	54.39	14.32, 14.31	14.15	73.5
4	$(C_2H_5O)_2P(O)CH(CN)(CH_3)_2$	146—147 (11)	1.4378	1.0551	54.49	54.39	13.96, 13.95	14.15	40.18
5	$(C_2H_5O)_2P(O)CH(CN)C_6H_{5-n}$	160—162 (10)	1.4378	1.0401	58.78	59.01	13.37, 12.98	13.30	49.38
6	$(C_2H_5O)_2P(O)CH(CN)CH_2CH=CH_2$	154 (10)	1.4482	1.0777	53.91	53.98	14.16	14.29	73.27
7	$(C_2H_5O)_2P(O)CH(CN)CH_2C_6H_5$	170—171 (1)	1.5000	—	—	—	11.16, 11.19	11.47	58.06
8	$(C_2H_5O)_2P(O)C(CN)(CH_2C_6H_5)_2$	210—215 (2)	1.5275	—	—	—	9.22, 9.13	8.68	—

TABLE 3

Serial No.	Formula	B.p. at pressure (mm)	n_D^{20}	d_4^{20}	MR_D		Analysis for P (%)		Yield (%)
					Found	Calc.	Found	Calc.	
1	$(C_2H_5O)_2P(O)C(CN)(C_2H_5)CH_2CH_2COOCH_3$	167° (2)	1.4490	1.1120	70.20	69.89	10.52, 10.83	10.65	90.6
2	$(C_2H_5O)_2P(O)C(CN)(C_2H_5)CH_2CH(CH_3)COOC_2H_5$	168 (1)	1.4480	1.0381	93.05	92.98	8.26, 8.23	8.58	75.16
3	$(C_2H_5O)_2P(O)C(CN)(CH_2CH=CH_2)(CH_2CH_2CN)$	175 (3)	1.4620	1.0977	67.63	67.55	11.54, 11.71	11.48	42.6
4	$(C_2H_5O)_2P(O)C(CN)(C_2H_5)CH_2CH_2CN$	180 (1.5)	1.4550	1.0669	72.73	72.64	11.00, 11.01	10.84	78.25

EXPERIMENTAL

Diethylphosphonoacetic acid nitrile was synthesized by a modified method [2]. Chloroacetonitrile was added dropwise to triethyl phosphite in an Arbuzov flask heated to 130-140°. The ethyl chloride formed was distilled off through a downward condenser. Distillation of the reaction mixtures gave diethylphosphonoacetic acid nitrile in 80-85% yields.

B.p. 126-127° at 2 mm, n_D^{20} 1.4310, d_4^{20} 1.1312, MR_D 40.52; calculated 40.59.
Found %: P 17.64, 17.65. $C_6H_{12}O_3NP$. Calculated %: P 17.52.

The literature gives b.p. 132-135° (1.2 mm), and other constants are not given [2].

General technique for the addition reactions between phosphonoacetic acid nitrile and unsaturated compounds. To an equimolecular mixture of phosphonoacetic acid nitrile (7-10 g) and the unsaturated compound, a saturated solution of sodium ethylate in anhydrous ethyl alcohol was gradually added dropwise. The reaction commenced, according to the nature of the unsaturated compound, after the addition of the catalyst in amounts varying from one to two drops to several milliliters. In some instances there was no heat evolution even after the addition of considerable amounts of the alcoholate. The reaction mass was then heated several hours on the boiling water bath and then distilled under vacuum (Table 1).

Synthesis of homologs of diethylphosphonoacetonitrile. To 4-7 g of finely chopped metallic potassium in a mixture of dry ether and dioxane, and equimolecular amount of the nitrile of phosphonoacetic acid was gradually added dropwise. The flask was heated on the water bath till all the potassium had reacted. This usually needed 1-2 hours. An alkyl halide (1.2-1.5 moles) was then gradually added to the potassium phosphonoacetonitrile solution, and the reaction mass heated with continuous stirring 3-6 hours on the water bath (the alkyl iodides react much more rapidly than the bromides). The precipitated salt (potassium bromide or iodide) was filtered off, the solvent was removed, and the residue distilled under vacuum (Table 2).

Addition of the nitrile of α-diethylphosphonobutyric acid to methyl acrylate. 7.8 g of the nitrile and 5 g of methyl acrylate was placed in a distillation flask fitted with a plate-type fractionating column. After the addition of 3 drops of saturated sodium ethylate solution a vigorous reaction commenced, accompanied by the evolution of considerable amounts of heat. To complete the reaction, the flask was heated 1 hour on the water bath, and this was followed by vacuum distillation. The yield was 9.6 g of the methyl ester of the of γ-diethylphosphono-γ--cyanocaproic acid (Table 3, Compound 1).

Addition of the nitrile of α-diethylphosphonovaleric acid to butyl methacrylate. Several drops of sodium ethylate were added to a mixture of 9.35 g of nitrile and 6.03 g of butyl methacrylate. The temperature of the mixture began to rise (to 55°) a few minutes after the catalyst addition. The reaction mixture was heated one hour and then distilled under vacuum. The yield was 5.8 g of the butyl ester of β-methyl-γ-diethylphosphono-γ--cyanoenanthic acid (Table 3, Compound 2).

Addition of the nitrile of α-diethylphosphono-β-vinylpropionic acid to acrylonitrile. The reaction was carried out with 8.5 g of the nitrile and 2.05 g of acrylonitrile, and proceeded very vigorously in the presence of sodium ethylate. The yield was 4.5 g of the dinitrile of α-diethylphosphono-α-allyl-glutaric acid (Table 3, Compound 3).

Addition of the nitrile of α-diethylphosphonocaproic acid to acrylonitrile. The reaction between 7.5 g of the nitrile and 2.5 g of acrylonitrile yielded 7.2 g of the dinitrile of α-(n-butyl)-α-diethylphosphonoglutaric acid.

SUMMARY

1. The nitriles of α-diethylphosphonopropionic, -butyric, -valeric, -isovaleric, -caproic, -vinylpropionic, and -phenylpropionic acids were synthesized by alkylation of the nitrile of phosphonoacetic acid by means of alkyl halides.

2. It was shown that the nitrile of phosphonoacetic acid and its homologs add on to unsaturated compounds of the electrophilic type in the presence of alkali metal alcoholates. A series of addition compounds with the esters and nitriles of αβ-unsaturated carboxylic acids was prepared.

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SOME TRANSFORMATIONS OF 1-AMINO-5,6,7,8-TETRAHYDRONAPHTHALENE-2--CARBOXYLIC ACID

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In one of our previous communications [1] it was mentioned that the 1-amino- and 4-amino-5,6,7,8-tetrahydronaphthalene-2-carboxylic acids obtained react in different ways with acetic anhydride. This is examined in greater detail in the present communication.

When 4-amino-5,6,7,8-tetrahydronaphthalene-2-carobxylic acid is heated with acetic anhydride it forms a compound with properties typical of acetyl derivatives of amino acids [1]. When 1-amino-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid is heated a short time with excess acetic anhydride, a compound with m.p. 122-124° is formed, insoluble in aqueous alkali, the elementary composition of which corresponds to the product formed by the removal of a molecule of water from acetylaminotetrahydronaphthalenecarboxylic acid.

It is known that the same compound is formed both when anthranilic acid is heated with excess acetic anhydride [2] and when a molecule of water is removed from N-acetylanthranilic acid – the so-called acetylanthranil which, according to the literature, is 2-methyl-3,1,4-benzooxazone [3].

In order to determine the structure of the substance with m.p. 122-124° which we prepared from 1-amino--5,6,7,8-tetrahydronaphthalene-2-carboxylic acid, its absorption spectrum in the ultraviolet region was studied. The figure shows the absorption spectra of this substance and of acetylanthranil*.

As the figure shows, the absorption spectra of acetylanthranil (I) and of the substance with m.p.122 124°(II) are very similar in form. The Curve (II) is somewhat displaced into the long wave region relative to Curve (I), which can be completely accounted for by the influence of the hydrogenated ring condensed with the aromatic ring. From a comparison of the absorption spectra of the two compounds it may be concluded that they both have the same system of conjugate double bonds. Since it is known that acetylanthranil has the benzooxazone type of structure, it may be concluded that the compound formed when 1-amino-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid is heated with excess acetic anhydride is 2-methyl-5,6-[1'2'-(5',6',7',8'-tetrahydronaphtho)]-3,1,4-oxazone.

By the action of aqueous caustic soda solution on 2-methyltetrahydronaphtho-3,1,4-oxazone we obtained 1--acetylamino-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid in a quantitative yield; the same acid is also formed by the action of acetyl chloride in pyridine on 1-amino-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid, but when the amino acid is heated with acetic acid, acetylation is accompanied by decarboxylation, and ar-a-acetylaminotetrahydronaphthalene is formed.

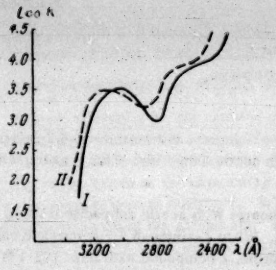
The formation of a hetero ring and the ease of CO_2 removal clearly show that the amino and the carboxyl groups in the original 1-amino-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid are joined to adjacent carbon atoms, and this once again confirms the validity of the earlier conclusion concerning the structure of this amino acid.

EXPERIMENTAL

2-Methyl-5,6,-[1',2'-(5',6',7',8'-tetrahydronaphtho)]-3,1,4-oxazone. 15 g of 1-amino-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid was heated 20 minutes with 30 ml of acetic anhydride at 80° bath temperature, and the resultant precipitate was filtered off. Acetic anhydride was removed under vacuum from the mother liquor to reduce the latter to a small volume, the precipitate was again filtered off, pressed, and dried. The total yield was 15.9 g (94%).

The substance was recrystallized from anhydrous ethyl alcohol. 2-Methyltetrahydronaphtho-3,1,4-oxazone is a colorless crystalline substance, m.p. 122-124°; it is soluble in ether, acetone, benzene, ethyl acetate, and dichloroethane, and is insoluble in water.

* The absorption spectrum of acetylanthranil is taken from the results of Zentmeyer and Wagner [3]; the absorption spectrum of 2-methyltetrahydronaphtho-3,1,4-oxazone was determined in the Physical Chemistry Laboratory of the All-Union Scientific Research Institute for Pharmaceutical Chemistry, under the guidance of Yu. N. Sheinker.



Absorption spectra of acetylanthranil (I) and 2-methyl-5,6-[1',2',-(5',6',7',8'-tetrahydronaphtho)]-3,1,4-oxazone (II).

Found %: C 72.78, 72.63; H 6.26, 6.26; N 6.43, 6.58 $C_{13}H_{13}O_2N$. Calculated %: C 72.54; H 6.09; N 6.51.

1-Acetylamino-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid. I. 12 g of 2-methyltetrahydronaphtho-3,1,4-oxazone was left to stand 2 days with a small excess of 5% caustic soda solution. The substance slowly dissolved. The solution was filtered, the filtrate acidified till acid to congo, and the precipitate filtered off and washed with water. The yield was 12.9 g. After recrystallization from dichloroethane, 1-acetylamino-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid is a colorless crystalline substance, m.p. 183-184° (decomp.); it is soluble in acetone and in methyl and ethyl alcohol, and in chloroform on warming.

Found %: C 67.21, 66.77; H 6.57, 6.51; N 5.72, 6.02. $C_{13}H_{15}O_3N$. Calculated %: C 66.93; H 6.48; N 6.00.

II. 1 g of 1-amino-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid was dissolved in 3 ml of pyridine and 0.41 g of acetyl chloride was added; heat evolution was noted. The reaction mixture was poured into water acidified with hydrochloric acid; the precipitate formed was recrystallized several times from dichloroethane; m.p. 184-185° (decomp.). A mixed sample with the acetyl amino acid prepared from 2-methyltetrahydronaphtho-3,1,4-oxazone showed no melting point depression.

The heating of 1-amino-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid with acetic acid. 1 g of the amino acid was heated 3.5 hours with 1 g of glacial acetic acid on the boiling water bath. The reaction mass was poured into water, and the precipitate was filtered off and recrystallized from ethyl acetate. The product had m.p. 158°, which agrees with the melting point of 1-acetylamino-5,6,7,8-tetrahydronaphthalene given in the literature. A mixed sample showed no depression of melting point.

SUMMARY

1. It was established that the action of acetic anhydride on 1-amino-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid results in the formation of 2-methyltetrahydronaphtho-3,1,4-oxazone, while acetic acid on heating yields ar-α-acetylaminotetrahydronaphthalene.

2. 1-Acetylamino-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid is formed by the action of acetyl chloride on the corresponding amino acid in pyridine solution, and also by the action of dilute alkali solution on 2-methyltetrahydronaphtho-3,1,4-oxazone.

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SYNTHESIS OF SOME NEW ESTERS OF GLUCOSE

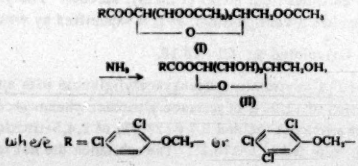
K. S. Bokarev and N. N. Melnikov

Selective herbicides are finding ever-increasing application in agriculture for combating weeds in sowings of a great variety of crops. 2,4-Dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and their various derivatives, which have a selective action on dicotyledons [1,2], have found particularly extensive application.

Despite the extensive scale on which these compounds are used, the mechanism of their action on plants is quite unknown, although various workers have put forward some hypotheses. Suggestions have been made both concerning the possibility that halophenoxyacetic acids react with individual functional groups of the plant cell, and the possibility that they react with the plant enzyme systems. The probability has also been pointed out that the physiological activity is due not to the halophenoxyacetic acids themselves, but to their conversion products in the plant [3-7]. However, these are all speculative suppositions and lack experimental confirmation.

In view of all this we undertook an investigation of the synthesis of various derivatives of 2,4-D and 2,4,5-T the formation of which is possible in the plant. We first attempted to synthesize esters of glucose, the main plant monosaccharide, on the assumption that the degree of physiological activity of such compounds might provide an indication of the possibility of their formation in the plant when it is treated with 2,4-D or 2,4,5-T.

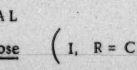
On the basis of extensive literature data on glucose esters of other acids, the most rational method for the synthesis of the hitherto undescribed esters of glucose and 2,4-dichlorophenoxyacetic and 2,4,5-trichlorophenoxyacetic acids is the reaction of their silver salts with acetobromoglucose, followed by removal of the acetyl groups by means of ammonia:



Such deacetylation by means of ammonia solution in methyl alcohol was successfully achieved by Robert and Tabone [8] for the preparation of glucose anthranilic acid ester from the corresponding tetraacetyl derivative. According to Freed [9], the acid chloride of 2,4-dichlorophenoxyacetic acid resembles the aromatic rather than the aliphatic acid chlorides. This gave reason to believe that when tetraacetyl-2,4-dichloro- and tetraacetyl--2,4,5-trichlorophenoxyacetylglucose (I) are treated with the calculated amount of ammonia solution in methyl alcohol, the acetyl groups will be removed first, and the required 2,4-dichloro- or 2,4,5-trichlorophenoxyacetylglucose (II) will be formed.

In reality, the last stage takes place with almost quantitative formation of 2,4-dichlorophenoxyacetamide and 2,4,5-trichlorophenoxyacetamide, which indicates that the 2,4-dichloro- and 2,4,5-trichlorophenoxyacetyl groups are preferentially removed before the acetyl groups. The results of the experiments indicate that the formation of 2,4-dichlorophenoxyacetyl- and 2,4,5-trichlorophenoxyacetylglucose in plants is unlikely.

EXPERIMENTAL

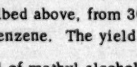
2,3,4,6-Tetraacetyl-1-(2',4'-dichlorophenoxyacetyl)glucose (I, R = ). A mixture of 30 g of finely ground silver 2,4-dichlorophenoxyacetate, 41.1 g of acetobromoglucose, and 150 ml of benzene was heated 10 hours to boiling with stirring. After cooling, the mixture was filtered. The residue from the filter was transferred to a flask and shaken with 200 ml of ether. The undissolved substance was filtered off and the ether extract was combined with the benzene solution. The solid was warmed twice with 100 ml of alcohol. All the extracts were combined and the solvent was removed under reduced pressure by means of the water-jet pump. The residue crystallized after removal of the solvent. The yield was almost quantitative. 8.4 g of the substance was recrystallized three times from 25 ml of methyl alcohol. The yield was 5.9 g. M. p. 125-126°, $[\alpha]_D^{20}$ + 7.4° (in dioxane). The ester belongs to the β-series, as it is saponified by emulsin.

Found %: Cl 12.63, 12.78. $C_{22}H_{24}O_{12}Cl_2$. Calculated: Cl 12.86.

Treatment of 2,3,4,6-tetraacetyl-1-(2',4'-dichlorophenoxyacetyl)glucose with ammonia solution in methyl alcohol. A suspension of 4.00 g of tetraacetyldichlorophenoxyacetylglucose in 32.46 ml of methyl alcohol containing 0.519 g of dry ammonia was shaken 12 hours. The crystals formed were filtered off, washed with a small amount of methyl alcohol, and dried. The yield was 0.77 g. M.p. 153°. The mother liquor was evaporated to dryness. The residue (2.75 g) was placed in a flask containing 20 ml of water and 50 ml of ether. The mixture was shaken 5 minutes. The undissolved substance was filtered off and dried. The yield was 0.45 g. M.p. 151°.

The ether layer was separated and evaporated to dryness. The residue weighed 0.3 g. M.p. 148°. None of the three substances produced a depression of melting point when mixed with the others. The total yield was 1.52 g (the theoretical yield is 1.60 g of 2,4-dichlorophenoxyacetamide). The substance was recrystallized from 20 ml of methyl alcohol. The yield was 1.1 g. M.p. 155°. According to the literature, 2,4-dichlorophenoxyacetamide melts at 155-156° [5]. A sample mixed with 2,4-dichlorophenoxyacetamide synthesized from 2,4-dichlorophenol and chloroacetamide showed no melting point depression.

Found %: N 6.55, 6.36. $C_8H_7O_2NCl_2$. Calculated %: N 6.36.

2,3,4,6-Tetraacetyl-1-(2',4',5',-trichlorophenoxyacetyl)glucose (I, R = ). This was prepared by a method analogous to that used for the ester described above, from 30 g of silver 2,4,5-trichlorophenoxyacetate, 41.1 g of acetobromoglucose, and 150 ml of benzene. The yield was 38.0 g (78.3%).

9 g of the ester was recrystallized three times from 50 ml of methyl alcohol. The yield was 6.5 g. M.p. 170-171°, $[\alpha]_D^{20}$ + 8.3° (in dioxane). The ester has β-configuration, as it is saponified by emulsin.

Found %: Cl 18.01, 17.95. $C_{22}H_{23}O_{12}Cl_3$. Calculated %: Cl 18.16.

Treatment of 2,3,4,6-tetraacetyl-1-(2',4',5'-trichlorophenoxyacetyl)glucose with ammonia solution in methyl alcohol. The treatment of a suspension of 11.90 g of tetraacetyltrichlorophenoxyacetylglucose with 70.24 ml of methyl alcohol containing 1.410 g of ammonia yielded 5.2 g (93.5%) of 2,4,5-trichlorophenoxyacetamide. M.p. 174°. According to the literature [5], m.p. is 174.5-175.5°. The substance did not lower the melting point of a previously prepared sample of the amide.

Found %: N 5.67, 5.75. $C_8H_6O_2NCl_3$. Calculated %: N 5.50.

SUMMARY

2,3,4,6-Tetraacetyl-1-(2',4'-dichlorophenoxyacetyl)glucose, and 2,3,4,6-tetraacetyl-1-(2',4',5'-trichlorophenoxyacetyl)glucose, not described previously, have been synthesized. It is shown that these compounds react with ammonia to form quantitative yields of 2,4-dichlorophenoxyacetamide and 2,4,5-trichlorophenoxyacetamide respectively.

The observations convincingly show that the formation of such glucose esters in plants treated with 2,4-D and 2,4,5-T is improbable.

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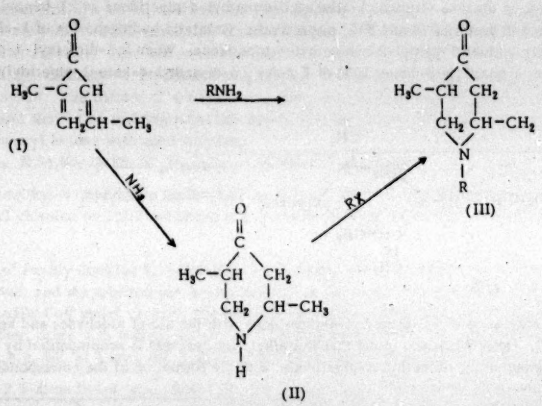
HETEROCYCLIC COMPOUNDS

XXXIII. SYNTHESIS OF 1-ALKYL-2,5-DIMETHYL-4-PIPERIDONES

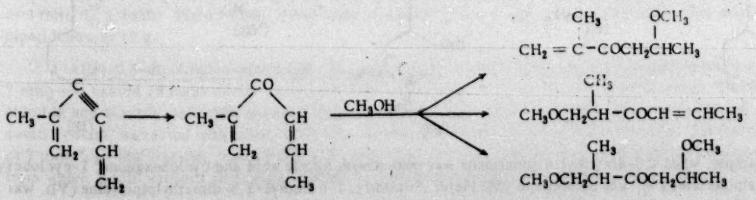
I. N. Nazarov, E. M. Cherkasova, N. S. Prostakov, and N. I. Shvetsov

In recent years systematic investigations were developed in our laboratory for the search for new analgesics, among which derivatives of the piperidine series occupy an important position. The starting materials for the synthesis of these substances are various γ-piperidones, which are easily prepared by means of a method based on acetylene, developed in our laboratory [1].

The present paper describes the preparation of 13 new 1-alkyl-2,5-dimethyl-4-piperidones (III), which were synthesized by two methods, illustrated by the following scheme:



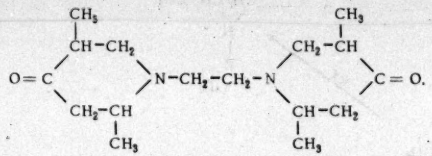
The action of primary lower amines (methyl-, ethyl-, propyl-, and n-butyl-amines) on propenyl isopropenyl ketone (I) readily yields the corresponding 1-alkyl-2,5-dimethyl-4-piperidones (III) in 60-80 % yields. For these reactions it is also possible to use methoxy ketones, formed by the addition of methanol to propenyl isopropenyl ketone during the hydration of vinylisopropenylacetylene in aqueous methanol solutions [2, 3].



The reaction between propenyl isopropenyl ketone and primary amines with heavy or branched radicals (isoamyl-, cyclohexyl-, and n-dodecylamines) proceeds less vigorously and leads, in the same conditions, to the formation of the corresponding 1- alkyl-2,5-dimethyl-4-piperidones (III) only in 30-50% yields.

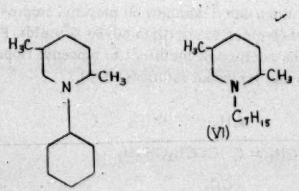
Worse results are obtained by the use, in such reactions with the higher amines, of the corresponding methoxy ketones instead of propenyl isopropenyl ketone. For example, the action of cyclohexylamine on propenyl isopropenyl ketone gave 1-cyclohexyl-2,5-dimethyl-4-piperidone in a yield of about 50%, but the reaction between cyclohexylamine and the corresponding methoxy ketones yielded the same piperidone in a yield of only about 15%. The interesting fact must be noted that the reaction between primary aminesand these methoxy ketones only proceeds readily in the presence of water, while in anhydrous conditions the reaction proceeds with difficulty and gives low yields of the corresponding piperidones. This influence of water on reactions between amines and β--methoxy ketones has been previously observed in other instances [4].

The 1-alkyl-2,5-dimethyl-4-piperidones (III) described above may be prepared not only by the reaction between propenyl isopropenyl ketone and primary amines, but also by the alkylation of 2,5-dimethyl-4-piperidone (II), which is formed by the action of ammonia on propenyl isopropenyl ketone and on the corresponding methoxy ketones [1]. When the lowest alkyl iodides (methyl, propyl, and n-butyl iodides) were heated with 2,5-dimethyl--4-piperidone (II) in dioxane solution, the corresponding 1-alkyl-2,5-dimethyl-4-piperidones (III) were formed in yields of about 60%. The same alkylation reaction occurs with greater difficulty with higher or branched alkyl iodides (isopropyl, isobutyl, isoamyl, n-hexyl, n-nonyl, and n-undecyl iodides) and gives 30-50% yields of the corresponding 1-alkyl-2,5-dimethyl-4-piperidones only with the use of catalysts (copper or bismuth salts). Alkyl bromides, and still more alkyl chlorides, are unsuitable for the alkylation of 2,5-dimethyl-4-piperidone by the above reaction in the conditions studied. However, chlorides of the allyl type, containing a mobile chlorine atom, may be successfully used for this purpose. For example, when 2,5-dimethyl-4-piperidone was heated with allyl chloride and benzyl chloride in dioxane solution, 1-allyl,-2,5-dimethyl-4-piperidone and 1-benzyl-2,5-dimethyl--4-piperidone were obtained in yields of 74 and 59%, respectively. Catalytic hydrogenation of 1-allyl-2,5-dimethyl-4-piperidone readily yielded 1-propyl-2,5-dimethyl-4-piperidone. When 2,5-dimethyl-4-piperidone was heated with dibromoethane, a small yield (about 10%) of 1,2-di-(2,5-dimethyl-4-keto-1-piperidyl)ethane (IV) was obtained.



(IV)

We also studied the alkylation of 2,5-dimethyl-4-piperidone with the aid of aldehydes and ketones in the presence of formic acid [5]. However, it was found that this alkylation reaction is accompanied by the simultaneous reduction of the carbonyl group in 2,5-dimethyl-4-piperidone, with the formation of the corresponding substituted piperidones.



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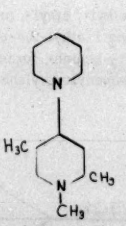
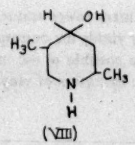
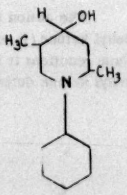
(VI)



(VII)



(VIII)



(IX)

For example, when 2,5-dimethyl-4-piperidone was heated with formic acid and cyclohexanone, 1-cyclohexyl--2,5-dimethylpiperidine (V), was obtained in 25% yield. Similarly, 1-n-heptyl-2,5-dimethylpiperidine (VI), was obtained in 15% yield by the heating of a mixture of 2,5-dimethyl-4-piperidone, enanthol, and formic acid. When 1,2,5-trimethyl-4-piperidone was heated with piperidine and formic acid, a small yield (about 3%) of 1,2,5-trimethyl--4-piperidylpiperidine (VII) was obtained. The above reaction gives more satisfactory results in the alkylation of

2,5-dimethyl-4-piperidol (VIII). As an example, we studied the alkylation of this piperidol by means of cyclohexanone and formic acid, and obtained 1-cyclohexyl-2,5-dimethyl-4-piperidol (IX) in 44% yield.

EXPERIMENTAL

1,2,5-Trimethyl-4-piperidone (III, R = CH_3). a) A mixture of the previously described [3] methoxy ketones obtained by hydration of vinylisopropenylacetylene in aqueous methanol and 340 g of 30 % aqueous methylamine solution was heated in a steel container for 6 hours at 65°.

The excess methylamine was removed under a slight vacuum, and 14% hydrochloric acid was added to the residue till it was acid to litmus. Neutral substances were removed by 2-fold extraction with ether. The aqueous solution of organic base hydrochlorides was treated with caustic potash to saturation, the oily layer of free bases which separated out was dissolved in ether, and the remaining aqueous layer was repeatedly extracted with ether. The ether extracts were combined, and, after being dried by sodium sulfate, the reaction product was twice distilled under vacuum. The yield was 179 g of 1,2,5-trimethyl-4-piperidone, b.p. 85-87° at 17 mm [1]. Yield 60%. 29 g of resinous residue remained after the distillation. The neutral ether extract yielded 5 g of the original methoxy ketones (b.p. 54-85° at 4 mm). 1.5 g of resinous residue remained after distillation of the neutral products.

b) To a solution of 20 g of methyl iodide in 35 ml of dioxane, 5 g of freshly distilled 2,5-dimethyl-4-piperidone (b.p. 73.5-74° at 9 mm, n_D^{20} 1.4670 [1]) was added with cooling and stirring. Heat was evolved, a precipitate formed, and the reaction mass became red. After addition of the piperidone the reaction mixture was heated 3 hours with vigorous boiling. 50 ml of water was then added to the cooled reaction mass, the layer of excess methyl iodide was separated off, and the remaining aqueous solution was treated with solid caustic potash till an oily layer of the amine separated out. This was extracted with ether, dried by sodium sulfate, and distilled under vacuum to yield 3.3 g of 1,2,5-trimethyl-4-piperidone with b.p. 56° at 6 mm, n_D^{20} 1.4614. 1 3 g of resinous residue remained after the distillation. The picrate of the 1,2,5-trimethyl-4-piperidone melted at 162° after two recrystallizations from alcohol, and showed no melting point depression with the picrate of the amine prepared by the cyclization of propenyl isopropenyl ketone with methylamine.

Found %: N 14.80, 14.88. $C_{14}H_{18}O_8N_4$. Calculated %: N 15.13.

1,2,5-trimethyl-4-piperidone methiodide melted at 179° after three recrystallizations from alcohol. The action of acetyl chloride on 1,2,5-trimethyl-4-piperidone yielded the chloroacetate in the form of colorless crystals, m.p. 102-103°.

c) 17 g of freshly distilled 2,5-dimethyl-4-piperidone was dissolved in 20 ml of dioxane, 15 g of dimethyl sulfate was added, and the solution was heated 3 hours on the water bath at 90-95°. At the end of the heating the dioxane was distilled off under vacuum, the product was diluted with water (35 ml), treated with caustic potash, extracted with ether, dried with sodium sulfate, and distilled under vacuum. The yield was 10.2 g of 1,2,5-trimethyl-4-piperidone, b.p. 54° at 5 mm, n_D^{20} 1.4611. 5.6 g of residue remained after the distillation.

1-Ethyl-2,5-dimethyl-4-piperidone (III, R = C_2H_5). 56 g of the methoxy ketones prepared by the hydration of vinylisopropenylacetylene in aqueous methanol solution (b.p. 50.67° at 10 mm), 20 g of ethylamine, and 10 ml of water was heated 5 hours at 80° in a steel ampoule. The contents of the ampoule were transferred to a flask, acidified with concentrated hydrochloric acid, the methanol was removed on the water bath under a vacuum produced by a water-jet pump, and the residue was extracted with ether to remove neutral products. A hydrochloric acid solution of the bases was saturated with alkali, extracted 5 times with ether, dried with sodium sulfate, and distilled under vacuum. The yield was 44.3 g of the previously described [2] 1-ethyl-2,5-dimethyl-4-piperidone, b.p. 76-78° at 6 mm, n_D^{20} 1.4630. Yield 72.5%. Total yield of neutral products was 3.5 g. The residue after distillation of the piperidone was 12 g.

1-Allyl-2,5-dimethyl-4-piperidone (III, R = C_3H_5). 77.5 g of 2,5-dimethyl-4-piperidone (b.p. 72-73° at 7 mm) was heated 18 hours on the water bath with 70 g of allyl chloride and 75 ml of dioxane. The unreacted allyl chloride and dioxane were then removed under vacuum. The residue was dissolved in water (50 ml), saturated with caustic potash, extracted with ether, dried with sodium sulfate, and distilled under vacuum: 1st fraction, b.p. 50-75° at 7 mm, 2 g; 2nd fraction, b.p. 75-86° at 7 mm, 75 g. The 2nd fraction was crude 1-allyl-2,5-dimethyl-4-piperidone, from which 3-fold vacuum distillation yielded 32 g of pure 1-allyl-2,5-dimethyl-4-piperidone.

B.p. 87° at 7.5 mm, n_D^{20} 1.4740, d_{20}^{20} 0.9464, MR_D 49.68; calculated 49.66.
Found %: N 8.02, 7.90. $C_{10}H_{17}ON$. Calculated %: N 8.38.

The picrate melted at 112-116° after 3 recrystallizations from alcohol.

1-Propyl-2,5-dimethyl-4-piperidone (III, R = C_3H_7). a) 70 g of 2,5-dimethyl-4-piperidone (b.p. 72-73° at 7 mm) was heated 17 hours on the boiling water bath with 52 ml of dioxane and 132 g of propyl iodide. The unreacted propyl iodide and dioxane were then removed under vacuum. The residue was dissolved in 10% hydrochloric acid (50 ml), the solution was extracted with ether and saturated with solid caustic potash, and the product was extracted with ether, dried with sodium sulfate, and distilled under vacuum. 50 g of crude 1-propyl-2,5-dimethyl-4-piperidone was obtained, b.p. 75-80°, from which 22.5 g of pure 1-propyl-2,5-dimethyl-4-piperidone was obtained after 3-fold vacuum distillation.

B.p. 88-89° at 8 mm, n_D^{20} 1.4602, d_{20}^{20} 0.9260, MR_D 50.01; calculated 50.13.
Found %: N 8.10, 7.85. $C_{10}H_{19}ON$. Calculated %: N 8.29.

The picrate melted at 157-158° (from alcohol).

b) 10 g of the 1-allyl-2,5-dimethyl-4-piperidone described above was hydrogenated over Raney nickel in a solution of 25 ml of alcohol. In 9 hours 1500 ml of hydrogen was absorbed (21°, 739 mm) as compared with the theoretical 1530 ml. The catalyst was filtered off, the alcohol distilled off, and the residue distilled under vacuum. The yield was 9 g of 1-propyl-2,5-dimethyl-4-piperidone, b.p. 87-90° at 7.5 mm. After two vacuum distillations this yielded 3.5 g of the pure substance, b.p. 88.5-89° at 7.5 mm, the picrate of which melted at 157-158° (from alcohol) and gave no melting point depression with the preceding sample.

c) 120 g of propylamine (b.p. 49-50°) was gradually added to 225 g of propenyl isopropenyl ketone (b.p. 47-50° at 12 mm) [3], and the mixture left overnight. The solution was then heated 4 hours at 60°, acidified with 150 ml of concentrated hydrochloric acid, and twice extracted with ether to remove neutral products. 15 g of the original propenyl isopropenyl ketone with b.p. 47-50° at 12 mm was obtained in this way. The hydrochloric acid solution of the base was saturated with alkali, the resultant oil was extracted with ether, dried with sodium sulfate, and distilled under vacuum. The yield was 247 g (71.5%) of 1-propyl-2,5-dimethyl-4-piperidone, b.p. 80-82° at 5 mm, the picrate of which melted at 157-158° and did not give a melting point depression with the preceding samples. The residue in the distillation flask was 40 g.

1-Isopropyl-2,5-dimethyl-4-piperidone (III, R = iso-C_3H_7). a) A mixture of 43 g of 2,5-dimethyl-4-piperidone, 43 ml of dioxane, and 62 g of isopropyl iodide was heated 10 hours on the boiling water bath in the presence of 2 g of copper sulfate. The dioxane and the unreacted isopropyl iodide were then driven off under vacuum. The residue was dissolved in hot water (150 ml), cooled, and saturated with solid caustic potash. The oil which separated was extracted with ether, dried with sodium sulfate, and distilled under vacuum: 1st fraction, b.p. 70-84° at 10 mm, 10 g; 2nd fraction, b.p. 84-87° at 10 mm, 18.5 g; 3rd fraction b.p. 87-110° at 10 mm, 2 g. The residue in the distillation flask was 4 g.

4-fold vacuum distillation of the second fraction yielded 11.5 g of 1-isopropyl-2,5-dimethyl-4-piperidone.

B.p. 86-87° at 8 mm, n_D^{20} 1.4635, d_{20}^{20} 0.9342, MR_D 49.87; calculated 50.13.
Found %: N 8.00. $C_{10}H_{19}ON$. Calculated %: N 8.29.

The picrate melted at 168° (from alcohol).

b) A mixture of 280 g of propenyl isopropenyl ketone and the corresponding methoxy ketones (b.p. 50-90° at 9 mm) and 180 g of 66% aqueous isopropylamine was heated 5 hours in a steel container at 70-75°. The reaction mass was then transferred to a round-bottomed flask, acidified with concentrated hydrochloric acid, and evaporated under vacuum. The residue was extracted with ether, saturated with alkali, extracted with ether, dried with sodium sulfate, and distilled under vacuum. The yield was 283 g of 1-isopropyl-2,5-dimethyl-4-piperidone, b.p. 75-80° at 3.5 mm. The residue in the distillation flask was about 10 g.

1-Butyl-2,5-dimethyl-4-piperidone (III, R = C_4H_9). a) 23.2 g butylamine and 25 ml of water was added to 70 g of propenyl isopropenyl ketone and the corresponding methoxy ketones (b.p. 57-70° at 8 mm). Much heat was evolved during the mixing. The solution was heated 3 hours at 60-80°, and the following day, after acidification with dilute hydrochloric acid (1:1) and extraction of the neutral products with ether, the aqueous solution of the amine hydrochloride was treated with alkali. The product was extracted with ether, dried with sodium sulfate, and distilled under vacuum. The yield was 49.4 g of 1-butyl-2,5-dimethyl-4-piperidone, b.p. 75-76° at 2 mm, n_D^{20} 1.4630. The fractions boiling below and above the piperidone totalled 9.9 g and the residue after distillation was 1.7 g. Distillation of the neutral products yielded 26.3 g of unreacted propenyl isopropenyl ketone. The residue was 2.8 g.

b) A solution of 63 g of 2,5-dimethyl-4-piperidone (b.p. 74° at 8 mm, n_D^{20} 1.4670) and 115 g of butyl iodide in 60 ml of dioxane was heated 13 hours with 4 g of copper sulfate at 90-95° with vigorous stirring. The reaction mixture was cooled, 100 ml of water was added, and the solution treated with caustic potash till a layer of the amine separated out; this was repeatedly extracted with ether, dried with sodium sulfate, and distilled three times under vacuum. The yield was 53.8 g of 1-butyl-2,5-dimethyl-4-piperidone in the form of a colorless liquid with a characteristic amine odor.

B.p. 80-81° at 3 mm, n_D^{20} 1.4630, d_{20}^{20} 0.9258, MR_D 54.53; calculated 54.75.
Found %: C 71.78, 71.90; H 11.53, 11.30. $C_{11}H_{21}ON$. Calculated %: C 72.13; H11.47.

The picrate melted at 135-136° after two recrystallizations from alcohol.

Found %: N 13.44, 13.40. $C_{17}H_{24}O_8N_4$. calculated %: N 13.59.
The methiodide consists of colorless crystals, m.p. 151.5° (from alcohol).
Found %: N 4.35, 4.40. $C_{12}H_{24}ONI$. Calculated %: N 4.30.

The butiodide of 2,5-dimethyl-4-piperidone was precipitated in the form of colorless crystals with m.p. 100-103° from an equimolecular mixture of the piperidone and butyl iodide.

The first runnings, consisting of a mixture of the original 2,5-dimethyl-4-piperidone with butyl iodide and dioxane, totalled 8.6 g; the residue after the distillation was 14 g.

1-Isobutyl-2,5-dimethyl-4-piperidone (III, R = iso-C_4H_9). a) A mixture of 33 g of 2,5-dimethyl-4-piperidone, 50 g of isobutyl iodide, and 27 g of calcined potash was heated 15 hours at 90-95° with vigorous stirring. Treatment analogous to that described in the preceding experiment yielded 21 g of 1-isobutyl-2,5-dimethyl-4--piperidone.

B.p. 80° at 3.5 mm, n_D^{20} 1.4605, d_{20}^{20} 0.9170, MR_D 54.79; calculated 54.75.
Found %: N 7.92, 7.92. $C_{11}H_{21}ON$. Calculated %: N 7.65.

The methiodide of 1-isobutyl-2,5-dimethyl-4-piperidone was obtained after two recrystallizations from alcohol in the form of colorless crystals, m.p. 147-148°.

Found %: N 4.20, 4.25. $C_{12}H_{24}ONI$. Calculated %: N 4.30.

b) A mixture of 450 g of propenyl isopropenyl ketone and the corresponding methoxy ketones (b.p. 50-65° at 10 mm), 200 g of isobutylamine, and 100 ml of water, was heated 4.5 hours at 70-80°. The reaction mass was then acidified with concentrated hydrochloric acid (200 ml), the oily layer was separated off, the hydrochloric acid solution was evaporated under vacuum, and the neutral products extracted with ether. The residue was saturated with alkali, extracted with ether, dried with sodium sulfate, and distilled under vacuum. The yield was 225 g of 1-isobutyl-2,5-dimethyl-4-piperidone, b.p. 85-90° at 5 mm. The neutral products yielded 45 g of methoxy ketones, b.p. 60-65° at 10 mm.

1-Isoamyl-2,5-dimethyl-4-piperidone (III, R = iso-C_5H_{11}). a) 20 g of 2,5-dimethyl-4-piperidone, 34.2 g of isoamyl iodide, and 50 ml of dioxane were stirred together 4.5 hours at 95° in the presence of 1.2 g of sublimed bismuth trichloride. The dioxane and the unreacted isoamyl iodide were then distilled off under vacuum. The residue was dissolved in 15% hydrochloric acid and extracted twice with ether to remove neutral products.

The hydrochloric acid solution was saturated with alkali, and the product was extracted with ether, dried with sodium sulfate, and distilled under vacuum; 1st fraction, b.p. 66-70° at 2 mm, 1.8 g; 2nd fraction, b.p. 84-86° at 2 mm, 11.5 g; 3rd fraction, b.p. 96-134° at 2 mm, 1 g.

The second fraction was crude 1-isoamyl-2,5-dimethyl-4-piperidone, from which the pure substance was obtained by 2-fold vacuum distillation.

B.p. 90-92° at 2 mm, n_D^{20} 1.4615, d_4^{20} 0.9102, MR_D 59.46; calculated 59.36.
Found %: N 7.63, 7.39. $C_{12}H_{23}ON$. Calculated %: N 7.1.

The picrate melted at 142.5-143° (from alcohol).

Found %: C 50.42; H 6.1; N 13.04, 13.16; $C_{18}H_{26}O_8N_4$. Calculated %: C 50.7; H 6.14; N 13.1.

b) 4.4 g of isoamylamine was gradually added to 6.4 g of propenyl isopropenyl ketone (b.p. 46-49° at 12 mm) with cooling and stirring. The solution was warmed 6 hours at 65°, and then treated as described in the preceding experiment. As the result of 2-fold vacuum distillation 4 g of 1-isoamyl-2,5-dimethyl-4-piperidone

was obtained, b.p. 83-85° at 1 mm, n_D^{20} 1.4613. The picrate melted at 142.5-143° (from alcohol) and showed no melting point depression in a mixed sample with the preceding substance.

1-n-Hexyl-2,5-dimethyl-4-piperidone (III, R = n-C_6H_{13}). 14 g of 2,5-dimethyl-4-piperidone, 31 g of n-hexyl iodide, 40 ml of dioxane, and 1.2 g of bismuth trichloride were stirred together 9.5 hours at 80°. The dioxane was then distilled off under vacuum. The residue was dissolved in 15% hydrochloric acid and extracted with ether to remove neutral products. The hydrochloric acid solution was saturated with alkali and the product was extracted with ether, dried with sodium sulfate, and distilled under vacuum. The yield was 12.5 g of crude 1-n-hexyl-2,5-dimethyl-4-piperidone, b.p. 111-115° at 3 mm, from which the pure substance was obtained by another vacuum distillation.

B.p. 114-115° at 3 mm, n_D^{20} 1.4615, d_4^{20} 0.9018, MR_D 64.36; calculated 63.99.
Found %: N 6.84, 6.78. $C_{13}H_{25}ON$. Calculated %: N 6.63.

The methiodide melted at 123-124°.

Found %: N 4.055. $C_{14}H_{28}ONI$. Calculated %: N 3.96.

1-Cyclohexyl-2,5-dimethyl-4-piperidone (III, R = C_6H_{11}). 21 g of cyclohexylamine (b.p. 130-150°) was gradually added with stirring to 23.5 g of propenyl isopropenyl ketone, and the solution was left overnight. 5 ml of water and 10 ml of methanol was then added to the reaction mixture, the solution heated 6 hours at 75-80°, and acidified with concentrated hydrochloric acid (25 ml). The methanol was driven off under slight vacuum, and the residue was twice extracted with ether to remove neutral products.

The hydrochloric acid solution was saturated with alkali, and then product was extracted with ether, dried with sodium sulfate, and distilled under vacuum: 1st fraction, b.p. 70-107° at 3.5 mm, 5 g; 2nd fraction, b.p. 108-120° at 3.5 mm, 26.5 g; residue in the distillation flask, 5 g.

By addition of 5 ml of ligroine (b.p. 80-100°) to the 2nd fraction, 10 g of 1-cyclohexyl-2,5-dimethyl-4-piperidone was isolated in the form of large colorless crystals, m.p. 73-74°. Repeated vacuum distillation of the uncrystallized oil yielded 12 g of a substance with b.p. 108-113°, from which a further 3 g of crystals with m.p. 73-74° was obtained by freezing.

The uncrystallized portion of the substance was converted into the hydrochloride by the passage of a stream of dry hydrogen chloride into an ether solution of the base. Recrystallization of the resultant precipitate from alcohol-ether mixture yielded 9 g of 1-cyclohexyl-2,5-dimethyl-4-piperidone hydrochloride, m.p. 171-172°. When an aqueous solution was treated with ammonia, the crystalline base was precipitated, with m.p. 73-74° (from ligroine), which did not give a depression of melting point with the preceding sample.

The total yield was therefore 20 g of 1-cyclohexyl-2,5-dimethyl-4-piperidone, m.p. 73-74°.

Found %: N 6.57, 6.77. $C_{13}H_{23}ON$. Calculated %: N 6.70.

The hydrochloride melted at 171-172° (from alcohol-ether mixture).

Found %: N 5.78, 6.04; Cl 14.50, 14.55. $C_{13}H_{24}ONCl$. Calculated %: N 5.73; Cl 14.48.

1-Benzyl-2,5-dimethyl-4-piperidone (III, R = $C_6H_5CH_2$). 87 g of 2,5-dimethyl-4-piperidone, 115 g of benzyl chloride and 87 ml of dioxane were heated together 16 hours on the boiling water bath. The dioxane was then removed under vacuum. The residue was dissolved in 10% hydrochloric acid (150 ml), the solution was extracted 3 times with ether, and saturated with caustic potash. The oil which separated was extracted with ether, dried with sodium sulfate, and distilled under vacuum: 1st fraction, b.p. 60-70° at 4 mm, 5 g; 2nd fraction, b.p. 89-123° at 4 mm, 16 g; 3rd fraction, b.p. 123-133° at 3 mm, 87 g; residue in the distillation flask, 10 g.

As the result of two vacuum distillations of the 3rd fraction, 84 g of 1-benzyl-2,5-dimethyl-4-piperidone was obtained.

B.p. 129-130° at 3.5 mm, n_D^{20} 1.5291, d_4^{20} 1.021, MR_D 65.53; calculated 65.00.
Found %: N 6.73, 6.70. $C_{14}H_{19}ON$. Calculated %: N 6.45.

The picrate melted at 142° (decomp.) from alcohol.

1-n-Nonyl-2,5-dimethyl-4-piperidone (III, R = n-C_9H_{19}). 17 g of 2,5-dimethyl-4-piperidone, 44 g of n-nonyl iodide, and 30 ml of dioxane were heated together 12.5 hours at 90°.

After the usual treatment 12.4 g of 1-n-nonyl-2,5-dimethyl-4-piperidone with b.p. 140-150° at 4 mm was obtained. The pure substance was obtained after a second distillation.

B.p. 146-148° at 4 mm, n_D^{20} 1.4615, d_4^{20} 0.8966, MR_D 77.56; calculated 77.84.
Found %: N 5.66, 5.50. $C_{16}H_{31}ON$. Calculated %: 5.53.

1-n-Undecyl-2,5-dimethyl-4-piperidone (III, R = n-$C_{11}H_{23}$). 10 g of 2,5-dimethyl-4-piperidone, 22.4 g of n-undecyl iodide, 20 ml of dioxane, and 1.5 g of bismuth triiodide were heated together 6 hours at 75-80° with vigorous stirring.

The usual treatment yielded 6.1 g of 1-n-undecyl-2,5-dimethyl-4-piperidone with b.p. 130-132° at 0.09 mm. The pure substance was obtained after a second distillation.

B.p. 127-128° at 0.09 mm, n_D^{20} 1.4660, d_4^{20} 0.889. MR_D 87.59; calculated 87.08.
Found %: N 5.10, 5.10. $C_{18}H_{35}ON$. Calculated %: N 4.97.

The residue after the distillation was 4.4 g.

1-n-Dodecyl-2,5-dimethyl-4-piperidone (III, R = n-$C_{12}H_{25}$). 18 g of n-dodecylamine was added to 12 g of propenyl isopropenyl ketone (b.p. 49-51° at 12 mm). Considerable heat was evolved and a homogeneous solution was formed. The reaction mass was then heated 6.5 hours at 60-70° and left overnight. After the usual treatment 6.8 g of 1-n-dodecyl-2,5-dimethyl-4-piperidone was obtained.

B.p. 129-132° at 0.09 mm (after a second vacuum distillation), n_D^{20} 1.4700, d_4^{20} 0.8900, MR_D 92.54; calculated 91.70.
Found %: N 4.59, 4.50. $C_{19}H_{37}ON$. Calculated %: N 4.74.

1-Methoxymethyl-2,5-dimethyl-4-piperidone (III, R = CH_2OCH_3). 17 g of chloromethyl ether in 50 ml of anhydrous ether was added dropwise to 27 g of 2,5-dimethyl-4-piperidone in 75 ml of anhydrous ether during half an hour. A considerable white precipitate of 2,5-dimethyl-4-piperidone hydrochloride was formed. After the mixture had stood one hour at room temperature the ether solution was decanted, the precipitate was washed with ether, and the ether extracts were combined and distilled under vacuum: 1st fraction, b.p. 45-52° at 2 mm, 1.7 g; 2nd fraction, b.p. 72-75° at 2 mm, 3.25 g; residue, 5 g.

The 2nd fraction was 1-methoxymethyl-2,5-dimethyl-4-piperidone.

B.p. 72-75° at 2 mm, d_4^{20} 0.9982, n_D^{20} 1.4788, MR_D 48.86; alculated 47.16.
Found %: N 7.47, 7.59. $C_9H_{17}O_2N$. Calculated %: N 8.18.

The picrate melted at 160-160.5° (from alcohol).

Found %: N 13.82. $C_{15}H_{20}O_9N_4$. Calculated %: N 13.97.

The precipitate of 2,5-dimethyl-4-piperidone hydrochloride which did not dissolve in ether was dissolved in water, saturated with alkali, extracted with ether, dried with sodium sulfate, and distilled under vacuum. The result was 15.4 g of the original 2,5-dimethyl-4-piperidone with b.p. 73-74° at 9 mm, n_D^{20} 1.4670, d_4^{20} 0.9704.

1,2-Di-(2,5-dimethyl-4-keto-1-piperidyl)ethane (IV). 10 g of freshly distilled 2,5-dimethyl-4-piperidone was heated with 57 g of ethylene bromide in the presence of 0.7 g of copper sulfate and 0.5 ml of water 7 hours on the boiling water bath. At the end of the heating the reaction mass was dissolved in 15 ml of water. The solution was subjected to the usual treatment with caustic potash and extraction of the free base with ether. Vacuum distillation of the reaction product yielded 2.5 g of the original 2,5-dimethyl-4-piperidone and 3.9 g of a very viscous, yellow liquid with b.p. 174° at 3 mm, which gradually crystallized. The yield was 1.1 g of 1,2-di-(2,5-dimethyl-4-keto-1-piperidyl)ethane (IV) in the form of colorless crystals which melted at 135-138° after recrystallization from anhydrous alcohol.

Found %: N 9.93, 9.73. $C_{16}H_{28}O_2N_2$. Calculated %: N 10.00.

1-Cyclohexyl-2,5-dimethyl-4-piperidol (IX). 4 portions of 98% formic acid, 0.8 g each, were added to a solution of 3.5 g of 2,5-dimethyl-4-piperidol (VIII) (m.p. 88-90° [6]) in 5.5 g of cyclohexanone during 1.5 hours. Violent evolution of carbon dioxide took place. The total amount of gas evolved during the reaction was 1 g, in comparison with the theoretical 1.1 g. The solution was then cooled to room temperature and saturated with dry hydrogen chloride; the precipitated crystals were filtered off and recrystallized from anhydrous alcohol. The yield was 3 g of 1-cyclohexyl-2,5-dimethyl-4-piperidol (IX) hydrochloride in the form of colorless crystals, m.p. 307-308°.

Found %: N 5.64, 5.76. $C_{13}H_{26}ONCl$. Calculated %: N 5.65.

The free base was prepared by the usual method from 1-cyclohexyl-2,5-dimethyl-4-piperidol hydrochloride, and consisted of colorless crystals with m.p. 85-86.5° (from ether).

Found %: N 6.57, 6.48. $C_{13}H_{25}ON$. Calculated %: N 6.54.

1-Cyclohexyl-2,5-dimethylpiperidine (V). A mixture of 20 g of 2,5-dimethyl-4-piperidone, 31 g of cyclohexanone, and 3.6 g of 98% formic acid was heated 15 minutes at 110-115°. 2.1g of carbon dioxide was evolved during that time; the mixture was then cooled and a further 3.6 g of formic acid was added, and the solution was heated half an hour at 115-117°. 1.8 g of carbon dioxide was evolved in that time. Such additions of formic acid (3.6 g portions) and heating (at 125-130°) were repeated 2 more times till evolution of carbon dioxide ceased (a further 0.8 g of carbon dioxide was evolved). 25 ml of methanol was then added to the cooled mass, and the solution was saturated with dry hydrogen chloride. The precipitate was filtered off and recrystallized from methanol. The yield was 9.3 g of 1-cyclohexyl-2,5-dimethylpiperidine (V) hydrochloride, m.p. 332-335°. A second recrystallization from methanol yielded the pure substance, with m.p. 334-335°.

Found %: N 5.66, 5.99; Cl 15.20, 15.00. $C_{13}H_{26}NCl$. Calculated %: N 6.05; Cl 15.35.

6 g of the hydrochloride was dissolved in water and treated with 50% caustic potash solution. The oil which separated out was extracted with ether, dried with sodium sulfate, and distilled under vacuum. The yield was 4.5 g of 1-cyclohexyl-2,5-dimethylpiperidine.

B.p. 83.5° at 2.5 mm, n_D^{20} 1.4855, d_4^{20} 0.9200, MR_D 61.60; Calculated 61.77.
Found %: C 79.86, 79.51; H 12.59, 12.58; N 7.58, 7.66. $C_{13}H_{25}N$. Calculated %: C 80.00; H 12.81; N 7.2.

1-n-Heptyl-2,5-dimethylpiperidine (VI). 10 g of 2,5-dimethyl-4-piperidone, 9 g of enanthol, and 1.2 g of 98% formic acid were mixed together at −10° and rapidly heated to 110° (before vigorous evolution of carbon dioxide commenced). After 15 minutes at 110° the reaction mass was cooled and a further 1.2 g of 98% formic acid was added. The mixture was then heated to 115° and held 20 minutes at that temperature till gas evolution ceased. 1.2 g of 98% formic acid was again added to the cooled mass and the solution was heated to 120°. As no more carbon dioxide was evolved, the reaction mass was cooled to room temperature and extracted 4 times with 10% hydrochloric acid (total 80 ml). The hydrochloric acid extracts were combined, extracted with ether, and saturated with caustic potash. The oil which separated out was extracted with ether, dried with sodium sulfate, and distilled under vacuum; 1st fraction, b.p. 40-80° at 3 mm, 2 g; 2nd fraction, b.p. 106-110° at 3 mm, 3 g; 3rd fraction, b.p. 113-118° at 3.5 mm, 3.9 g.

3-fold vacuum distillation of the 2nd and 3rd fractions yielded 2.5 g of 1-heptyl-2,5-dimethylpiperidine (VI).

B.p. 96.5-97.5° at 2 mm, n_D^{20} 1.4650, d_4^{20} 0.9132.
Found %: N 6.76, 6.68. $C_{14}H_{29}N$. Calculated %: N 6.64.

1,2,5-Trimethyl-4-piperidylpiperidine (VII). 20 g of 1,2,5-trimethyl-4-piperidone, 28.8 g of piperidine and 18 g of 98% formic acid were heated together 3 hours at 117-125°. During this time 3.1 g of carbon dioxide was evolved, as compared with the theoretical 6.2 g . 60 ml of concentrated hydrochloric acid was then added to the reaction mass. The solution was left overnight, heated 1 hour at the boil, and saturated with caustic potash. The oil which separated out was extracted with ether, dried with sodium sulfate, and distilled under vacuum. Repeated vacuum distillation yielded 1 g of 1,2,5-trimethyl-4-piperidylpiperidine (VII) in the form of a yellowish-green liquid.

B.p. 119.5-120° at 9.5 mm, n_D^{20} 1.4923, d_4^{20} 0.9324, MR_D 65.38; calculated 65.71.
Found %: N 12.11, 12.29. $C_{13}H_{26}N_2$. Calculated %: N 13.32.

The bis(methiodide) melted at 211-212.5° (from alcohol).

Found %: N 5.50, 5.45. $C_{15}H_{32}N_2I_2$. Calculated %: N 5.67.

SUMMARY

13 new 1-alkyl-2,5-dimethyl-4-piperidones were synthesized by the cyclization of propenyl isopropenyl ketone with various amines, and by the alkylation of 2,5-dimethyl-4-piperidone by alkyl halides.

It was established that the yields in these reactions decrease with increase in the molecular size, and with branching of the hydrocarbon chains of the corresponding amines and halides.

It was found that the action of carbonyl compounds and formic acid and 2,5-dimethyl-4-piperidone results in the formation of 2,5-dimethylpiperidines substituted in the 1-position with reduction of the keto group in the 4-position.

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PSEUDOTHIOHYDANTOINS AND THIOHYDANTOINS

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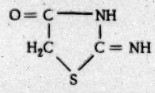
Pseudothiohydantoins and thiohydantoins are isomeric heterocyclic compounds with the formula $C_3H_4ON_2S$. Two of them belong to thiazolidine derivatives, and two others to imidazolidine derivatives: pseudothiohydantoin (I) or 2-iminothiazolidone-4 [1, 2], 2-thiohydantoin (II) or 2-thionoimidazolidone-4 [3],



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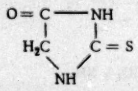

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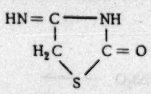

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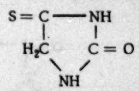


(IV)

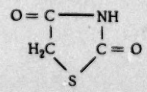
isopseudothiohydantoin (III)or 4-iminothiazolidone-2 [4], and 4-thiohydantoin (IV), or 4-thionoimidazolidone-2 [5].

Of the above substances, pseudothiohydantoin and 2-thiohydantoin have acquired the greatest importance, as their derivatives are used in the synthesis of amino acids [6] and also as sensitive reagents for inorganic analysis [7]. In the chemical literature the pseudothiohydantoins were often termed thiohydantoins [8, 9] which led to confusion. The recent literature shows that the question of isomerism was clearly raised even in 1881 [10], and it remains important to the present time, especially as pseudothiohydantoin has become significant as an antithyroid substance [11].

Pseudothiohydantoin is usually prepared by the condensation of chloroacetic acid with thiourea, The isomeric 2-thiohydantoin can be prepared by heating the hydrochloride of glycine ethyl ester with potassium thiocyanate. In contrast to this, L. M. Kulberg [12] described the condensation of thiourea with chloroacetic acid to form 2-thiohydantoin which decomposes at 250°.

Our purpose was to determine the direction of the condensation reaction between thiourea and chloroacetic acid by making use of transformations of the reaction products, as pseudothiohydantoin and 2-thiohydantoin do not have definite melting points.

According to the method described by Kulberg [12], we heated thiourea and chloroacetic acid in aqueous solution on the water bath (80-90°) till a negative reaction with potassium ferrocyanide was given. The product was neutralized by soda, and the precipitate formed was filtered off. As pseudothiohydantoin is partly soluble in water, not the precipitate but the filtrate was used. Concentrated hydrochloric acid was added to the filtrate in 1: 1 ratio and the mixture was evaporated on the water bath to a small volume. The crystals which formed were filtered off and recrystallized from a small amount of water (with the addition of active carbon). The melting point of the product, 125°, indicated the presence of thiazolidinedione (V).



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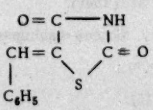
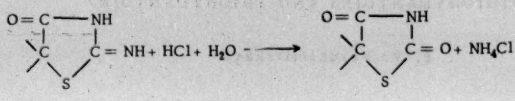


(VI)

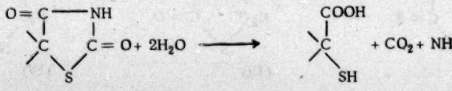
An attempt was made to condense thiourea with chloroacetic acid in glacial acetic acid. For this purpose a solution of chloroacetic acid in glacial acetic acid was boiled 15 minutes with the equivalent amount of thiourea, when a white precipitate was formed (2-thiohydantoin is a substance with a yellow color). 1 g-equivalent of benzaldehyde was added to the mixture, and the boiling was continued another hour. The reaction product was then cooled and neutralized by ammonia, and the precipitate was filtered off and washed with water. The precipitate was then boiled 10 hours with 10 times its own amount of concentrated hydrochloric acid under a reflux condenser. The crystals which formed were filtered off, washed with water, dried in air, and recrystallized from isoamyl acetate. The result was a colorless crystalline substance with m.p. 240°, which indicates [13] the presence of 5-benzylidenethiazolidinedione (VI).

The formation of thiazolidinedione and 5-benzylidenethiazolidinedione proves that the condensation product of thiourea with chloroacetic acid is certainly pseudothiohydantoin and not 2-thiohydantoin. Thiazoldinedione and its benzylidene derivative were formed according to the equation:



It should be pointed out that the direct conversion of 2-thiohydantoin into thiazolidinedione is impossible.

The identity of the substances obtained with thiazolidinedione and its 5-benzylidene derivative was also proved by qualitative reactions [14, 15]. Alkaline hydrolysis of thiazolidinedione and 5-benzylidenethiazolidinedione [16] yielded thioglycolic and benzylidenethioglycolic acid respectively, which could not be formed from 2-thiohydantoin.



The presence of thioglycolic acid was shown by the formation of a violet-red complex, and that of benzylidenethioglycolic acid, by the formation of a green-yellow iron-ammonium complex.

It is my duty to express my gratitude to N. M. Turkevich for valuable discussions of the work.

SUMMARY

1. The condensation reaction between thiourea and chloroacetic acid occurs in aqueous solutions with the formation of pseudothiohydantoin, and not of 2-thiohydantoin, as was proved by conversion of the product into thiazolidinedione.

2. The analogous condensation reaction in glacial acetic acid also leads to the formation of pseudothiohydantoin. After the addition of benzaldehyde and hydrolysis of the reaction product by means of hydrochloric acid, 5-benzylidinethiazolidinedione was obtained.

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CONDENSATION OF o-AMINOPHENYL MERCAPTANS WITH KETONES

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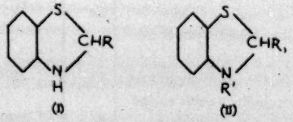
The condensation of aldehydes with o-aminophenyl mercaptans has been studied by a number of workers. Hofman [1] obtained 2-methylbenzothiazole by heating o-aminophenyl mercaptan with acetaldehyde. He, and later others [2-4], showed that the condensation yields benzothiazolines (I), which are very easily oxidized to the corresponding benzothiazole derivatives. The oxidation occurs in the air even during recrystallization of benzothiazolines, which makes them difficult to isolate. The condensation products of aldehydes with N-alkyl-o-aminothiophenols (II),



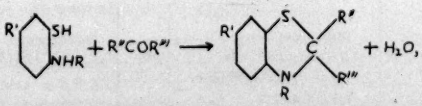
(I) (II)

which were prepared by Z. N. Pazenko [5], on the contrary, proved very stable to the action of atmospheric oxygen.

The condensation of ketones with o-aminophenyl mercaptans has practically not been studied. Kreysa and his co-workers [6] condensed o-aminothiophenol with methyl benzyl ketone. However, as the condensation was carried out in harsh conditions (6 hours at 250°), only the thermal decomposition products from the initially formed benzothiazoline were isolated. L. K. Mushkalo [7] condensed o-aminothiophenol with an unsaturated ketone, mesityl oxide, and obtained a derivative of dihydrobenzohepta-1,5-thiazine.

We studied the condensation of ketones, diketones, and acetoacetic ester with o-aminothiophenol, N-methyl--o-aminothiophenol, and 5-nitro-2-aminothiophenol. We also studied some chemical properties of the benzothiazolines formed by the condensation of o-aminophenyl mercaptans with ketones.

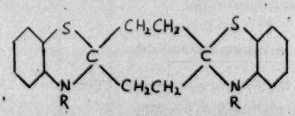
The condensation follows the simple scheme:



where R = H or CH_3, R' = H or NO_2, R'' and R''' = alkyls, aryls, or $CH_2COOC_2H_5$.

In most instances the condensation proceeds easily and with good yields. The reaction already begins at room temperature and to complete it, it is usually enough to heat the mixture 1-2 hours on the boiling water bath. Only the aromatic ketones need to be heated above 100°.

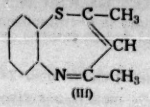
With diketones (cyclohexanedione-1,4, acetylacetone) condensation occurs at both carbonyl groups. The product

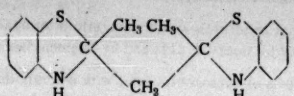


TABLE

Starting substances		Benzothiazolines formed			
aminothiophenols	ketones	name	yield (%)	boiling point, at pressure (mm)	melting point
o-Aminothiophenol	Acetone	2,2-Dimethylbenzothiazoline	84	142–143° (5)	45°
	Di-n-propyl ketone	2,2-Di-n-propylbenzothiazoline	47	186–188 (5)	–
	Cyclopentanone	2,2-Tetramethylenebenzothiazoline	63	–	55
	Cyclohexanone	2,2-Pentamethylenebenzothiazoline	73	–	111–112
	Acetophenone	2-Methyl-2-phenylbenzothiazoline	65	252–253 (20)	–
	Cyclohexanedione-1,4	1,4-Di-(benzothiazolinylidene)cyclohexane	63	–	233–234
	Acetylacetone	Di-(2-methylbenzothiazolinyl-2)methane	64	125–127 (8)	–
	Acetoacetic ester	2-Methyl-2-carboethoxymethylbenzothiazoline	77	190–192 (15)	–
N-Methyl-o-aminophenol	Acetone	2,2,3-Trimethylbenzothiazoline	84	125–130 (8)	–
	Diethyl ketone	2,2-Diethyl-3-methylbenzothiazoline	63	140–142 (8)	–
	Methyl n-propyl ketone	2,3-Dimethyl-2-n-propylbenzothiazoline	73	145–147 (10)	–
	Di-n-propyl ketone	2,2-Di-n-propyl-3-methylbenzothiazoline	50	140–142 (7)	–
	Cyclopentanone	2,2-Tetramethylene-3-methylbenzothiazoline	83	178–180 (13)	–
	Cyclohexanone	2,2-Pentamethylene-3-methylbenzothiazoline	73	166–168 (10)	35
	Acetophenone	2,3-Dimethyl-2-phenylbenzothiazoline	50	–	68
	o-Tolylacetone	2,3-Dimethyl-2-o-methylbenzylbenzothiazoline	50	145–150 (8)	–
	p-Tolylacetone	2,3-Dimethyl-2-p-methylbenzylbenzothiazoline	50	150–153 (8)	–
	Cyclohexanedione-1,4	1,4-Di-(N-methylbenzothiazolinylidene)-cyclohexane	80	–	220
	Acetylacetone	Di-(2,3-dimethylbenzothiazolinyl-2)methane	40	150–155 (10)	–
	Acetoacetic ester	2,3-Dimethyl-2-carboethoxymethylbenzothiazoline	51	180–182 (25)	–
2-Amino-5-nitrothiophenol	Acetone	2,2-Dimethyl-6-nitrobenzothiazoline	83	–	130–131
	Cyclopentanone	2,2-Tetramethylene-6-nitrobenzothiazoline	60	–	144–145
	Acetoacetic ester	2-Methyl-2-carobethoxy-methyl-6-nitrobenzothiazoline	60	–	95

is probably a mixture of cis- and trans- isomers. These were not separated. With acetylacetone another course of the reaction could also be expected, namely the formation of 7-membered heterocyclic ring (III). Such a seven-membered ring was obtained by Thiele and Steimig by the condensation of o-phenylenediamine with acetylacetone [8]. However, the substance obtained by us formed a di-silver salt and a dibenzoyl derivative, which is only possible if two mobile hydrogen atoms are present in the molecule. Both in its chemical properties and by its analytical results the condensation product of o-aminothiophenol and acetylacetone agreed with Formula (IV).


(III)


(IV)

The benzothiazolines synthesized are listed in the table.

The benzothiazolines are pale yellow oils or crystalline substances. They are weak bases and dissolve only in concentrated mineral acids. Benzothiazolines are precipitated when solutions in concentrated hydrochloric acid are diluted with water. The benzothiazolines are soluble in most organic solvents.

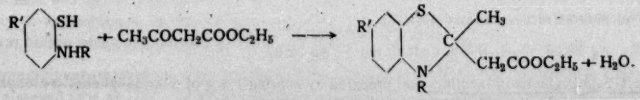
Benzothiazolines which have a nitro group in the benzene ring and a hydrogen atom with the nitrogen dissolve in alkalies to give a red color, and are separated out unchanged by acidification.

The benzothiazolines which do not have a radical at the nitrogen atom are converted into 2-alkylbenzothiazoles when heated to 250-260°. For example, 2,2-dimethylbenzothiazoline decomposes into 2-methylbenzothiazole and benzene. This reaction occurs analogously to the thermal decomposition of 2,2-dialkylbenzimidazolines, which was studied by Elderfield [9].

When heated with alcoholic alkali, benzothiazolines and N-methylbenzothiazolines decompose quantitatively to form o-aminophenyl mercaptans. Concentrated acids also destroy the thiazoline ring on boiling. The disulfides of o-amino-thiophenol and 5-nitro-2-aminophenol (m.p. 93 and 237-238° respectively) were obtained in almost quantitative yields by prolonged boiling of 2,2-dimethylbenzothiazoline and of 6-nitro-2,2-dimethylbenzothiazoline without protection from the air.

Benzothiazolines which do not contain radicals at the nitrogen atom are easily alkylated by means of alkyl iodides. When 2,2-dimethylbenzothiazoline was heated 30 minutes with methyl iodide in a sealed tube on the water bath, 2,2,3-trimethylbenzothiazoline was formed. Benzothiazolines without radicals at the nitrogen atom can be acetylated and benzoylated, and form silver derivatives. The latter are prepared by the action of silver nitrate solution in alcoholic ammonia on solutions of the benzothiazoline in alcohol. They are colorless or slightly yellow solids which dissolve with great difficulty in organic solvents.

The condensation of o-aminophenyl mercaptans with acetoacetic ester requires separate consideration. Rogers and Sexton [10] condensed acetoacetic ester with 2,2'-diaminodiphenyl disulfide, and obtained 2-acetonylbenzothiazole, 2-methylbenzothiazole, and 2 acetyl-3-keto-2,3-dihydrobenzothiazine-1,4. We condensed acetoacetic ester with o-aminothiophenol, N-methyl-o-aminothiophenol, and 5-nitro-2-aminothiophenol. In all three cases the reaction was found to proceed in only one direction:



This course of the reaction is proved by the following experiments.

The condensation product of acetoacetic ester with the o-aminophenyl mercaptan was cautiously saponified by heating it with dilute alkali. After acidification with hydrochloric acid, the oil was extracted with ether and distilled under vacuum. The product was 2,2-dimethylbenzothiazoline, with b.p. 142-143°, m.p. 45°, the benzoyl derivative of which melted at 156-157°. When the same condensation product was heated to 200°, thermal decomposition resulted in the formation of 2-methylbenzothiazole, which was identified by the methiodide and by the styryl dye, with an absorption maximum at 530 mμ, which is formed from 2-methylbenzothiazole methiodide by condensation with p-dimethylaminobenzaldehyde.

Thus, o-aminothiophenol condenses with acetoacetic ester analogously to o-aminophenol, the condensation products of which were studied by Hantzsch [11] and by Niementowski [12].

The condensation products of acetoacetic ester with o-aminothiophenol and 5-nitro-2-aminothiophenol form silver derivatives and acyl derivatives, but the condensation product with N-methyl-o-aminothiophenol does not form such derivatives.

EXPERIMENTAL

2,2-Dimethylbenzothiazoline. 5 g of o-aminophenyl mercaptan and 2.8 g of acetone were heated together 1 hour on the water bath in a sealed tube. The contents of the tube were treated with 10% caustic soda solution, the oil was extracted with ether, dried by calcium chloride, and distilled under vacuum. The thick oil obtained by the distillation (b.p. 142-143° at 5 mm) quickly crystallized. M.p. 45°, yield 5 g (76%).

Found %: N 8.37, 8.53. $C_9H_{11}NS$. Calculated %: N 8.48.

The silver derivative was prepared by the action of silver nitrate in alcoholic ammonia on an alcohol solution of the thiazoline. The mixture was diluted with water and the precipitate was filtered off. The yield was quantitative, m.p. 259-260°. The precipitate was washed with water, alcohol, and ether, and analyzed without crystallization.

Found %: Ag 39.36. $C_9H_{10}NSAg$. Calculated %: Ag 39.70.

The benzoyl derivative was prepared by the Schotten-Baumann reaction. After recrystallization from alcohol the m.p. was 156-157°.

Found %: N 5.22, 5.21. $C_{16}H_{15}ONS$. Calculated %: N 5.20.

The methylation of 2,2-dimethylbenzothiazoline was carried out by heating 1 g of 2,2-dimethylbenzothiazoline and 0.92 g of methyl iodide in a sealed tube 1 hour on the water bath. The yield was 0.5 g of a yellowish oil with b.p. 140° at 10 mm. It was identical with 2,2,3-trimethylbenzothiazoline prepared by the condensation of N-methyl-o-aminothiophenol with acetone.

Found %: N 7.70, 7.75. $C_{10}H_{13}NS$. Calculated %: N 7.82.

The decomposition of 2,2-dimethylbenzothiazoline was carried out as follows: 2 g of 2,2-dimethylbenzothiazoline was heated 3 hours at 250° in a Wurtz flask (with the thermometer in the liquid). 0.8 g of oil, which proved to be 2-methylbenzothiazole, was distilled off. The picrate melted at 148-149°.

2,2-Di-n-propylbenzothiazoline was prepared by heating a mixture of 1 g of di-n-propyl ketone and 1.1 g of o-aminophenyl mercaptan 1 hour on the water bath. The yield was 0.9 g (47%) of a yellowish oil, b.p. 186-188° at 5 mm.

Found %: N 6.20, 6.24. $C_{13}H_{19}NS$. Calculated %: N 6.33.

The silver derivative decomposed at 310°.

Found %: Ag 32.58. $C_{13}H_{18}NSAg$. Calculated %: Ag 32.92.

2-Methyl-2-phenylbenzothiazoline was prepared by heating 1.7 g of o-aminophenyl mercaptan and 1.7 g of acetophenone 3 hours at 130°. The yield was 2 g (65%), b.p. 252-255° at 20 mm.

Found %: N 6.12, 6.05. $C_{14}H_{13}NS$. Calculated %: N 6.16.

The silver derivative decomposed at 264°.

Found %: Ag 32.50. $C_{14}H_{12}NSAg$. Calculated %: Ag 32.33.

The thermal decomposition of 2-methyl-2-phenylbenzothiazoline at 250-260° yielded benzene (b.p. 80°, n_D^{20} 1.5015) and 2-methylbenzothiazole (picrate m.p. 148-149°).

2,2-Tetramethylenebenzothiazoline was prepared from a mixture of 2.58 g of o-aminophenyl mercaptan and 1.73 g of cyclopentanone. The reaction started even in the cold. After the mixture was heated 1 hour on the water bath, 3 g of a colorless crystalline substance was obtained. It was recrystallized from 70% alcohol. After recrystallization the yield was 2.5 g (63%), silky needles, m.p. 55°.

Found %: N 7.18, 7.39. $C_{11}H_{13}NS$. Calculated %: N 7.33.

The silver derivative decomposed at 212°.

Found %: Ag 36.05. $C_{11}H_{12}NSAg$. Calculated %: Ag 36.24.

The benzoyl derivative forms silky needles, m.p. 154-155°.

Found %: N 4.63, 4.65. $C_{18}H_{11}ONS$. Calculated %: N 4.74.

2 2-Pentamethylenebenzothiazoline was prepared from 2.2 g of o-aminophenyl mercaptan and 1.76 g of cyclohexanone by heating mixture 1 hour at 100°. After recrystallization from alcohol it forms silky needles, m.p. 111-112°, yield 2.4 g (66%).

Found %: N 6.73, 6.75. $C_{12}H_{15}NS$. Calculated %: N 6.82.

The silver derivative decomposed at 225°.

Found %: Ag 34.58. $C_{12}H_{14}NSAg$. Calculated %: Ag 34.61.

The benzoyl derivative forms needles, m.p. 114° (from 70% alcohol).

Found %: N 4.44, 4.38. $C_{19}H_{19}ONS$. Calculated %: N 4.53.

1,4-Di(benzothiazolinylidene)cyclohexane was prepared from 1.1 g of cyclohexanedione-1,4 and 2.45 g of o-aminophenyl mercaptan in the same manner as the two preceding compounds. After crystallization from glacial acetic acid (the substance is badly soluble in organic solvents) the yield was 2 g (63%). It forms needles, m.p. 233-234°.

Found %: N 8.62, 8.56. $C_{18}H_{18}N_2S_2$. Calculated %: N 8.58.

The silver derivative does not decompose below 300°.

Found %: Ag 39.70. $C_{18}H_{16}N_2S_2Ag_2$. Calculated %: Ag 40.00.

The benzoyl derivative has m.p. 266-267° (from glacial acetic acid).

Found %: N 5.46. $C_{32}H_{26}O_2N_2S_2$. Calculated %: N 5.24.

Di-(2-methylbenzothiazolinyl-2)methane was prepared from 1 g of acetylacetone and 2.5 g of o-aminophenyl mercaptan by heating them 3 hours at 100°. It is a yellow oil, b.p. 125-127° at 8 mm, yield 2 g (64%).

Found %: N 8.99, 8.90. $C_{17}H_{18}N_2S_2$. Calculated %: N 8.91.

2,2,3-Trimethylbenzothiazoline was prepared from 2 g of N-methyl-o-aminothiophenol and 0.87 g of acetone by heating them 1 hour on the water bath. The yield was 2.1 g (81%) of a yellowish oil with b.p. 140° at 10 mm.

Found %: N 7.70, 7.75. $C_{10}H_{13}NS$. Calculated %: N 7.82.

When the product was boiled with alcoholic alkali, N-methyl-o-aminothiophenol was obtained in 60% yield. The same N-methyl-o-aminophenol, identified as the disulfide with m.p. 68°, was obtained when 2,2,3-trimethylbenzothiazoline was boiled with concentrated hydrochloric acid.

2,2-Diethylmethylbenzothiazoline. 1.39 g of N-methyl-o-aminothiophenol was heated with 0.86 g of diethyl ketone 6 hours in a sealed tube at 110°. The yield of the thiazoline was 1.3 g (63%), b.p. 140-142° at 8 mm.

Found %: N 6.51, 6.62. $C_{12}H_{17}NS$. Calculated %: N 6.76.

2,3-Dimethyl-2-n-propylbenzothiazoline was obtained by heating 1.39 g of N-methyl-o-aminothiophenol with 0.86 g of methyl n-propyl ketone 3 hours on the water bath. It is a yellowish oil, b.p. 145-147° at 10 mm, yield 1 g (50%).

Found %: N 6.92, 6.83. $C_{12}H_{17}NS$. Calculated %: N 6.76.

2,2-Di-n-propyl-3-methylbenzothiazoline was obtained by heating 1.39 g of N-methyl-o-aminothiophenol with 1.14 g of di-n-propyl ketone 6 hours at 110°. The yield was 1.15 g (50%), b.p. 140-152° at 5 mm.

Found %: N 5.81, 5.82. $C_{14}H_{21}NS$. Calculated %: N 5.95.

2,2-Tetramethylene-3-methylbenzothiazoline was obtained by heating 2 g of N-methyl-o-aminothiophenol with 1.2 g of cyclopentanone 4 hours at 100°. It is a yellowish oil, b.p. 178-180° at 13 mm. Yield 2.5 g (83%).

Found %: N 6.52, 6.57. $C_{12}H_{15}NS$. Calculated %: N 6.82.

2,2-Pentamethylene-3-methylbenzothiazoline was obtained by heating 2 g of N-methyl-o-aminothiophenol with 1.41 g of cyclohexanone 1 hour at 100°. Yield 2.3 g (73%), b.p. 166-168° at 10 mm. The substance crystallized on standing. After recrystallization from alcohol, m.p. 35°.

Found %: N 6.48, 6.45. $C_{13}H_{17}NS$. Calculated %: N 6.39.

2,3-Dimethyl-2-phenylbenzothiazoline was prepared by heating a mixture of 1.39 g of N-methyl-o-aminothiophenol and 1.2 g of acetophenone 2 hours at 150°. After 2-fold crystallization from alcohol it forms colorless crystals, m.p. 68°. Yield 1.2 g (50%).

Found %: N 5.73, 5.80. $C_{15}H_{15}NS$. Calculated %: N 5.80.

2,3-Dimethyl-2-o-methylbenzylbenzothiazoline was prepared by heating 0.5 g of N-methyl-o-aminothiophenol and 0.5 g of o-tolylacetone 2 hours at 110°. It is a pale yellow oil, b.p. 85-87° at 8 mm, yield 0.4 g (38%).

Found %: N 5.13, 5.11. $C_{17}H_{19}NS$. Calculated %: N 5.20.

2,3-Dimethyl-p-methylbenzylbenzothiazoline was prepared in the same conditions from 0.5 g of N-methyl-o-aminothiophenol and 0.5 g of p-tolylacetone. The yield was the same. B.p. 150-153° at 8 mm.

Found %: N 5.34, 5.14. $C_{17}H_{19}NS$. Calculated %: N 5.20.

1,4-Di-(N-methylbenzothiazolinylidene)cyclohexane was prepared by heating 0.2 g of cyclohexanedione-1, with 0.5 g of N-methyl-o-aminothiophenol 1 hour at 100°. It forms colorless needles; after crystallization from alcohol, m.p. 220°. Yield 0.4 g (64%).

Found %: N 8.07, 8.15. $C_{20}H_{22}N_2S_2$. Calculated %: N 7.90.

Di-(2,3-dimethylbenzothiazolinyl-2)-methane was prepared by heating a mixture of 2.78 g of N-methyl-o-aminothiophenol and 1 g of acetylacetone 5 hours at 100°. The yield was 2.5 g (36%) of a yellowish oil, b.p. 150-155° at 10 mm.

Found %: N 7.96, 7.86. $C_{19}H_{22}N_2S_2$. Calculated %: N 8.18.

2,2-Dimethyl-6-nitrobenzothiazoline. The reaction between acetone (0.35 g) and 2-amino-5-nitrothiophenol (0.35 g) began in the cold and was completed after 30 minutes heating on the water bath. The product was recrystallized from 50% alcohol. The yield was 1 g (83%) of orange-yellow needles, m.p. 130-131°.

Found %: N 13.22, 13.30. $C_9H_{10}O_2N_2S$. Calculated %: N 13.33.

The silver derivative decomposes above 300°.

Found %: Ag 34.25. $C_9H_9N_2SAg$. Calculated %: Ag 34.06.

The acetyl derivative was prepared by boiling the product with acetic anhydride. M.p. 127-128° (from alcohol). It forms yellow plates, insoluble in alkalies.

Found %: N 10.95, 11.00. $C_{11}H_{12}O_3N_2S$. Calculated %: N 11.11.

When 2,2-dimethyl-6-nitrobenzothiazoline was boiled with concentrated hydrochloric acid, 2-amino-5-nitrothiophenol was formed, identified as the disulfide, m.p. 237-238°.

2,2-Tetramethylene-6-nitrobenzothiazoline was prepared by heating a mixture of 0.5 g of 5-nitro-2-aminothiophenol and 0.25 g of cyclopentanone 15 minutes at 100°. The condensation product was purified by dissolving it in alkali followed by precipitation by acid, and then recrystallized from 50% alcohol. Yield 0.4 g (60%).

It forms yellow needles, m.p. 144-145°.

Found %: N 11.67, 11.72. $C_{11}H_{12}O_2N_2S$. Calculated %: N 11.86.

The silver derivative decomposes at 230°.

Found %: Ag 31.65. $C_{11}H_{11}O_2N_2SAg$. Calculated %: Ag 31.49.

The acetyl derivative forms yellow crystals, m.p. 107-108°.

Found %: N 10.05, 10.15. $C_{13}H_{14}O_2N_2S$ Calculated %: N 10.06.

2-Methyl-2-carboethoxymethylbenzothiazoline. 3.4 g of o-aminothiophenol was heated with 3.1 g of acetoacetic ester 3 hours at 100°. The yield was 5 g (77%) of a yellowish oil, b.p. 190-192° at 15 mm.

Found %: N 5.76, 6.06. $C_{12}H_{15}O_2NS$. Calculated %: N 5.90.

The silver derivative decomposes at 227°.

Found %: Ag 31.02. $C_{12}H_{14}O_2NSAg$. Calculated %: Ag 31.39.

The benzoyl derivative forms silky needles, m.p. 155-156° (from alcohol).

Found %: N 4.55, 4.50. $C_{19}H_{19}O_3NS$. Calculated %: N 4.28.

2,3-Dimethyl-2-carboethoxymethylbenzothiazoline. 1.39 g of N-methyl-o-aminothiophenol was heated with 1.14 g of acetoacetic ester 3 hours at 100°. The product was a viscous yellowish oil with b.p. 180-182° at 25 mm. Yield 1.3 g (51%).

Found %: N 5.59, 5.56. $C_{13}H_{17}O_2NS$. Calculated %: N 5.57.

2-Methyl-2-carboethoxymethyl-6-nitrobenzothiazoline. 1 g of 5-nitro-2-aminothiophenol was heated with 0.77 g of acetoacetic ester 30 minutes at 100°. After crystallization from alcohol 1 g (60%) of brown crystals, m.p. 95°, was obtained.

Found %: N 9.87, 9.83. $C_{12}H_{14}O_4N_2S$. Calculated %: N 9.93.

The silver derivative is a yellow powder which decomposes at 194-195°.

Found %: Ag 27.00. $C_{12}H_{13}O_4N_2SAg$. Calculated %: Ag 27.24.

SUMMARY

The condensation of o-aminophenyl mercaptan, N-methyl-o-aminophenyl mercaptan, and 5-nitro-2-aminophenyl mercaptan with ketones, including cyclohexanedione-1,4, acetylacetone, and acetoacetic ester, has been studied.

23 benzothiazolines were prepared, and also a number of their derivatives – silver, acetyl, and benzoyl derivatives. It is shown that benzothiazolines are readily decomposed by alkalies and acids, and when heated above 250° decompose to form benzothiazole derivatives.

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REACTION OF IODINE CHLORIDE IN HYDROCHLORIC ACID SOLUTION WITH BARBITURIC ACID DERIVATIVES. I.

Ya. A. Fialkov and L. I. Rapaport

Numerous papers deal with the reactions between iodine chloride and unsaturated organic compounds. These reactions were mainly studied in nonaqueous, organic solvents or in absence of solvents, and much less in aqueous media. According to the literature, the nature of the reactions between iodine chloride and unsaturated compounds, and the structure of the reaction products, depend on the nature of the organic substance, the solvent, and the reaction conditions. For example, it was shown that ICl adds on at the double bond to propylene [1], isobutylene [2], styrene [3], asymmetrical diphenylethylene [4], etc., in accordance with the Markovnikov rule, but contrary facts are also known [4, 5]. Moreover, the addition reactions are often complicated by the subsequent removal of HCl or HI from the chloroiodination products, and the HI evolved is oxidized by excess iodine chloride [4]; if the reactions are carried out in an aqueous medium, hydrolytic effects are possible [4-8].

We considered it of interest to study the action of iodine chloride on barbituric acids containing hydrocarbon radicals*, with the use of 0.1 N solution of iodine chloride in hydrochloric acid, prepared according to Lang [9] and Gengrinovich [10] by the interaction of KI, KIO_3, and hydrochloric acid.

Iodine chloride in hydrochloric acid solution is in the form of the complex acid $HICl_2$ in equilibrium with its dissociation products: $HICl_2 \rightleftharpoons H^+ + ICl_2^-$; $ICl_2^- \rightleftharpoons I^+ + 2Cl^-$. The presence of I^+ and Cl^- in the reaction medium makes it possible to use such solutions of iodine chloride for bringing about a variety of reactions—oxidation, replacement of hydrogen in organic compounds, addition at double bonds, and complex formation [11, 12]. Reactions with unsaturated organic compounds have been described in less detail [11, 13].

The present communication gives the results of a study of the reactions of iodine chloride in hydrochloric acid solution with barbituric acids containing allyl or β-bromoallyl radicals at the carbon in position 5. The presence of electronegative groups in molecules of unsaturated compounds retards the addition of ICl to the latter, while in the presence of two such groups the reaction does not occur at all [8]; it was therefore of interest to determine the effect of the heterocyclic nucleus in barbituric acid and of the bromine atom in the allyl radical on these reactions.

1. Diallylbarbituric acid. It might be expected that the allyl radicals in this barbiturate would react in the same way as in allyl alcohol with iodine chloride. However, the literature data on this and other similar reactions are often contradictory.

Henry [14], by the action of iodine chloride on allyl alcohol, obtained the chloroiodo compound $CH_2OHCHICH_2Cl$, which was converted into an epichlorohydrin by the action of caustic potash. Bigot [15] obtained, by distillation of the reaction products of aqueous iodine chloride solution and allyl alcohol, a mixture of unreacted allyl alcohol, the chloroiodo compounds $CH_2OHCHICH_2Cl$ and $CH_2OHCHClCH_2I$, and the corresponding epichloro-and epiiodohydrins.

In his investigation of the addition of ICl to cinnamic acid and the subsequent hydrolysis of the chloroiodo product, Erlenmeyer [6] concluded that iodohydrin can be obtained only from α,β-unsaturated acids, when the formation of a hydrolyzable lactone is possible:

$$C_6H_5CH{=}CHCOOH \xrightarrow{+ICl} C_6H_5CHClCHICOOH \xrightarrow{-HCl}$$

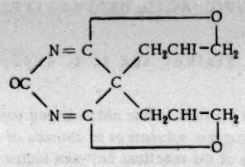
$$\longrightarrow C_6H_5CH(-O-)CHI-CO \xrightarrow{+H_2O} C_6H_5CHOHCHICOOH.$$

According to Ingle [7], the hydrolysis of compounds containing chlorine and iodine at secondary carbon atoms, $-CHClCHI-$, may, according to the nature of the substance and the reaction conditions, be accompanied by the removal of HCl, or HI, or both, with the formation of the following groups: $-CHOHCHI-$, $-CHClCHOH-$, $-CHOHCHOH-$,

* Barbiturates of this type include a number of widely used medical products. Another aim of the present investigation was to develop conditions for a new iodometric method for the quantitative analysis of these products.

respectively. However, Böeseken and Gelber [8] confirmed Erlenmeyer's proposed mechanism for the hydrolysis of chloroiodo derivatives.

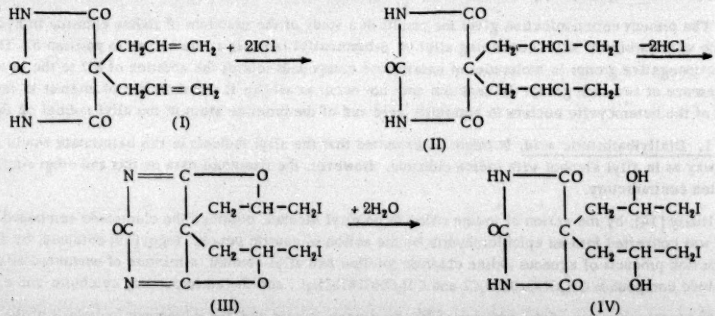
Bougault and Guillou [16], by action of iodine solution on diallylbarbituric acid in sodium bicarbonate solution, isolated a reaction product which, according to their data, is an iodolactone •,



formed as the result of IOH addition followed by removal of water. The product of this reaction, after washing with $NaHSO_3$ solution and recrystallization from alcohol, was obtained as a white powder which was insoluble in water and in alkali solutions, that is, this substance did not have acid properties.

In our experiments, when 0.1 N hydrochloric acid solution of iodine chloride was added to 0.8% aqueous diallylbarbituric acid solution, a copious precipitate was formed, while the ICl solution was decolorized. Quantitative investigations showed that for each mole of the barbiturate, 2 moles (4 g-equiv.) of ICl participate in the reaction, and 2 moles of HCl are evolved. The reaction product, after recrystallization from hot alcohol and drying at 70-80°, was a white crystalline powder, insoluble in water, soluble in hot alcohol and chloroform. At 213-215° it decomposed with evolution of iodine vapor. When the substance was boiled with alcoholic solution of caustic potash and silver nitrate was then added, a yellow precipitate of silver iodide was formed with only a slight admixture of silver chloride. The iodine content agreed with the formula $C_{10}H_{14}O_5N_2I_2$.

On the basis of the above literature data and our results it may be supposed that the reaction between diallylbarbituric acid and iodine chloride in hydrochloric acid solution proceeds according to the equations:



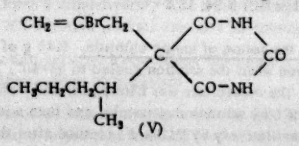
Firstly iodine chloride is added at the allyl radical double bonds (I) with the formation of a chloroiodo derivative (II). It seems likely, contrary to the views of Bougault and Guillou, that the halogens are added in agreement with the Markovnikov rule. This is to be explained by the influence of the ring system in barbituric acid, which plays the role of an electronegative group; as a result I^+ is directed to the outer, most highly hydrogenated, carbon atom. In our opinion, removal of HCl from the tautomeric form of the chloroiodo derivative leads to the formation of the corresponding lactone (III). The latter is hydrolyzed and forms the iodohydrin of diallylbarbituric acid (IV). For confirmation, an experiment was carried out to prepare the chloroiodo derivative of diallylbarbituric acid in absence of water; use was made of Erlenmeyer's method [6] for the preparation of α-iodo-β-chloro-β-phenyl- propionic acid from cinnamic acid. For this purpose Erlenmeyer used the complex acid $HICl_2$, which was extracted from iodine chloride in hydrochloric acid solution by means of ether.

• The paper by Bougault and Giullou does not describe the method of preparation and gives no analytical results.

By the action of a mixture of ICl and $HICl_2$ on diallylbarbituric acid it was possible to obtain its chloroiodo derivative (II), in the form of a white crystalline powder, insoluble in water and dilute acids, soluble with difficulty in chloroform, and easily in alkali solutions. When heated it decomposes with evolution of iodine vapor at 157-159°.

As was mentioned earlier, according to Bougault and Guillou a lactone is formed by the action of iodine solution on diallylbarbituric acid in the presence of $NaHCO_3$. This assertion appeared doubtful, as the results of our experiments showed that such a lactone is easily hydrolyzed. The experiment of Bougault and Guillou was therefore repeated. The substance obtained was identical in its external properties, decomposition temperature, solubility, acid properties, and iodine content, with the substance prepared with the aid of iodine chloride, so that it was not an iodolactone, as Bougault and Guillou stated, but the iodohydrin of diallylbarbituric acid.

2. Experiments with β-bromoallyl barbiturates. Barbiturates of this type used in medicine usually have one β-bromoallyl group at the carbon atom in position five; the second substituent at this carbon atom is usually an unsaturated hydrocarbon radical. We could find no information in the literature concerning the reactions of iodine chloride with such organic compounds. At the same time it is known [8] that the presence of halogens at carbon atoms linked by double bonds hinders further halogen addition.

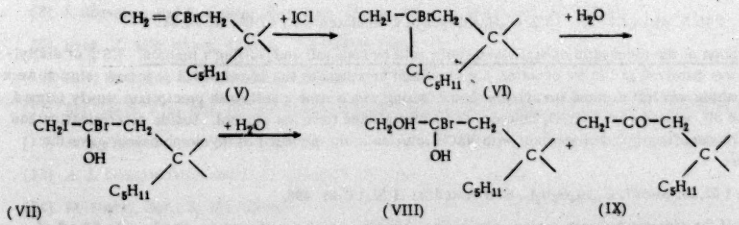


(V)

In the investigations described, sec-amyl-(β-bromoallyl)barbituric acid (V) (known as "rectone") was used. No appreciable action took place on the addition of a hydrochloric acid solution of iodine chloride to rectone at room temperature. In hot solutions (70-80°) the liquid became brown and iodine was evolved, and could be extracted with chloroform. The amount of iodine formed depended on the duration of the action, and increased upon repeated extraction of the iodine by chloroform. The iodine was extracted completely only in the course of 20-24 hours, but if excess sodium thiosulfate solution was added, in 15-20 minutes. The acidity of the solution increased at the same time. On the basis of these results it was supposed that in the conditions described ICl is added at the double bond of the bromoallyl radical, and this is followed by hydrolysis of the product, subsequently accompanied by evolution of iodine.

To verify this, the intermediate product which is extracted by chloroform together with iodine was isolated. Analysis of this product showed that a) it contains only traces of chlorine, which indicates practically complete removal of chlorine, evidently as HCl; b) bromine and iodine are present in approximately equivalent amounts, but less than the theoretical amounts calculated for rectone iodohydrin; this indicates partial removal of bromine and iodine, evidently as HBr and HI; c) the hydrogen iodide formed is oxidized by iodine chloride, and iodine is evolved.

From these experimental results it was concluded that the substance is a mixture of rectone iodohydrin and the products of various degrees of hydrolysis, and the results gave reason to believe that the following reactions take place between rectone and iodine chloride in hydrochloric acid solution: •



(V) (VI) (VII) (VIII) (IX)

The first product of the addition of ICl to rectone, (VI), is gradually hydrolyzed. The first, and rapid, step is the removal of chlorine and formation of rectone iodohydrin (VII); this is followed by slow removal of bromine and iodine with formation of a dihydroxy bromo derivative (VIII) and an iodoacetone derivative (IX).

Analogous results (of a qualitative nature) were obtained by the action of iodine chloride in hydrochloric acid

• Only part of the structure of the barbituric acid derivatives is shown in the equations.

solution on isopropyl-(β-bromoallyl)barbituric acid.

EXPERIMENTAL

1. Preparation of a hydrochloric acid solution of iodine chloride. 1 liter of 0.1 N ICl solution in 0.4 N hydrochloric acid* was prepared from stoichiometric amounts of KI (5.54 g) and KIO_3 (3.5 g), 40 ml of HCl (d 1.19) and water to 1 liter. The amount of ICl in the solution was determined by the addition of KI to a definite volume of the solution and titration of the iodine liberated according to the equation KI + ICl = KCl = I_2. The HCl in the decolorized solution was determined by titration with alkali solution in the presence of methyl orange.

2. Study of the reaction between diallylbarbituric acid and iodine chloride. About 0.2 g of the barbiturate (accurately weighed) was dissolved with warming in 100 ml of water, the solution was cooled, and 50 ml of 0.1 N solution of ICl in hydrochloric acid was added. After 10 minutes the excess ICl and the HCl formed were determined as described above.

0.0936, 0.1583 g sub.: combined with ml of 0.1 N ICl: 17.85, 29.16; ml of 0.1 N HCl evolved: 8.75, 15.04. Calculated ml: 0.1 N ICl: 17.98, 30.6; 0.1 N HCl 8.94, 15.3**.

3. Preparation of iodohydrin of diallylbarbituric acid by the action of iodine chloride. 0.40 g of diallylbarbituric acid was dissolved with warming in 50 ml of water, and when the solution cooled to 35-40°, 100 ml of 0.1 N hydrochloric acid solution of iodine chloride was added. The precipitate was filtered off and washed with a weak solution of hydrochloric acid to a negative reaction for ICl (KI solution and starch), and then with water to a neutral reaction to methyl orange. Iodine was determined quantitatively by Volhard's method after the substance had been boiled with alcoholic caustic potash solution.

Found %: I 51.8, 51.1. $C_{10}H_{14}O_5N_2I_2$. Calculated %: I 51.17.

4. Preparation of chloroiodoallylbarbituric acid. 15 ml of 1 N hydrochloric acid solution of iodine chloride was twice extracted with 10 ml of ether. The ether layer was separated off and dehydrated by calcium chloride. The ether solution was placed in a porcelain basin into a vacuum desiccator containing sulfuric acid and caustic potash. After evaporation of the ether a red-brown liquid remained, analysis of which showed it to be a mixture of ICl and $HICl_2$ in a molar ratio of 3:1.

0.8 g of diallylbarbituric acid (rather less than 1 mole per 2 moles of ICl) was added to the liquid. The yellow-orange solid mass which formed was treated with chloroform and then washed with chloroform on a glass filter. The chloroform solution contained excess ICl, the remaining unreacted barbiturate, and part of the chloroiodo, derivative. The residue on the filter was a white powder which was dried in a vacuum desiccator.

For halogen determination the substance was boiled with alcoholic solution of caustic potash. The total chlorine and iodine was determined by Volhard's method, and iodine was also determined separately by titration with $AgNO_3$ solution with an external indicator—paper moistened with $NaNO_2$ and starch solutions.

Found %: I 45.5, 45.2; Cl 12.1, 12.2. $C_{10}H_{12}O_3N_2Cl_2I_2$. Calculated %: I 47.61; Cl 13.31.

5. Preparation of the iodohydrin of diallylbarbituric acid by Bougault and Guillou's method. 0.8 g of diallylbarbituric acid was dissolved in 120 ml of water, 5 g of sodium bicarbonate and 20 ml of 0.1 N iodine solution were added, and the whole was left to stand twenty-four hours, during which time a yellowish precipitate slowly formed. This was filtered off, washed with $NaHSO_3$ solution, and recrystallized from hot alcohol. Iodine determination and titration of the product (suspended in alcohol) with NaOH solution in the presence of thymolphthalein gave the following results:

Found %: I 51.13. M 497. $C_{10}H_{14}O_5N_2I_2$. Calculated %: I 51.17. M 496.

6. Study of the reaction between rectone and iodine chloride. To 0.4 g of rectone dissolved in 20 ml of 0.1 N caustic soda solution, 200 ml of boiling water and 40 ml of 0.1 N hydrochloric acid solution of iodine chloride were added and the mixture left 1 hour, after which the liberated iodine was extracted with chloroform. $Na_2S_2O_3$ solution was added to the combined chloroform extracts till they were decolorized, the chloroform layer was separated off, washed with water and shaken with sodium sulfate to remove water, after which the chloroform was distilled off. The residue after removal of the chloroform was a white powder, insoluble in water, soluble in alcohol

* According to Gengrinovich [10], a hydrochloric acid solution of iodine chloride is stable 4-6 months when the ratio of HCl and ICl concentrations is ≥ 4.

** On the assumption that 1 mole of diallylbarbituric acid combines with 2 moles of ICl, and 2 moles of HCl are evolved.

and ether. When $AgNO_3$ solution was added to an aqueous alcohol solution of this substance acidified with nitric acid, silver halides were precipitated, iodine was liberated on addition of potassium iodide, and chloramine solution liberated first iodine and then bromine.

For quantitative argentometric determination of the halogens, the substance was boiled with alcoholic caustic potash solution • and water was added to a definite volume. The following were then titrated in equal aliquot portions: a) sum of I^-, Br^-, and Cl^-, by Volhard's method, b) sum of I^- and Br^- in the presence of sodium eosinate indicator, c) I^-, with external indicator.

Specimen determination. 0.3285 g substance; ml of 0.1 N $AgNO_3$ taken: a) 10.5, b) 10.5, c) 5.3. Calculated ml 0.1 N $AgNO_3$. $C_{12}H_{17}O_3N_2ClBrI$: a) 20.5, $C_{12}H_{18}O_4N_2BrI$: b)14.2,c)7.1.

SUMMARY

1. It was established that, in the reaction of a hydrochloric acid solution of iodine chloride with diallylbarbituric acid, iodine chloride is first added on at the allyl radical double bonds, and then the reaction product is hydrolyzed to form a diiodohydrin. The same substance is formed by the action of iodine in sodium bicarbonate solution. The ICl addition product can only be obtained in the absence of water.

The reaction between hydrochloric ICl solution and diallylbarbituric acid may be used for the quantitative iodometric determination of the latter.

2. When iodine chloride in hydrochloric acid solution acts on barbiturates containing β-bromoallyl radicals at the carbon atom in position five, ICl is also added at the double bond; the reaction product is hydrolyzed, chlorine being split off completely and rapidly, and bromine and iodine much more slowly. A mixture of several substances is formed, and therefore this reaction cannot form the basis for the quantitative determination of the corresponding barbituric acid derivatives.

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Ministry of Health Ukrainian SSR

• This method is used for the determination of bromine in rectone [17].

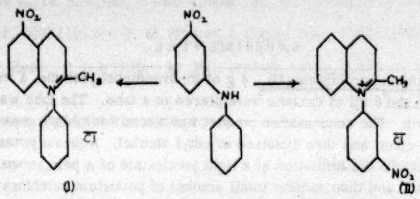
INVESTIGATIONS OF CYANINE DYES

VI. N-m-NITROPHENYLQUINALDINIUM PERCHLORATE AND ITS TRANSFORMATIONS

G. T. Pilyugin and Z. Ya. Krayner

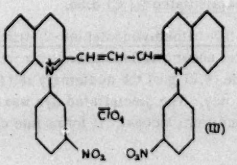
Quaternary salts of nitrogen-containing heterocyclic compounds with aryl radicals at the nitrogen atom in the ring are less readily available than the alkyl-substituted analogs. The explanation is that the free bases do not form salts with aryl halides or aryl esters of aromatic sulfonic acids according to the general, known method for the synthesis of haloalkylates of heterocyclic compounds. We prepared, for the first time, N-phenylquinaldinium perchlorate, from which quinocyanines with phenyl radicals were obtained [1].

This paper presents the results of work on the condensation of m-nitrodiphenylamine with paraldehyde, and the conversion of the quinaldinium salts formed into cyanine dyes of symmetric and asymmetric structure. In the case of m-nitrodiphenylamine the cyclization could proceed in two directions: a) at the position vicinal to the nitro group with the formation of N-phenyl-5-nitroquinaldinium chloride (I), or b) with the formation of a condensed pyridine nucleus with unsubstituted phenyl group (II):



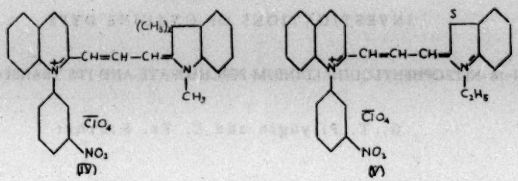
Experiments showed that, in condensation conditions, cyclization proceeds in the direction of formation of a quaternary N-m-nitrophenylquinaldinium salt (II). The other isomeric quaternary salt was not found. A proof for the above structure of the quaternary salt is the value of the absorption maximum of the symmetrical carbocyanine (III) obtained from it (613 mμ) which differs very little from the absorption maximum of a similar dye with an unsubstituted phenyl radical at the nitrogen atom (614 mμ). This is in full agreement with the previously established fact that substituents in the phenyl radical at ring nitrogen atoms have little influence on the optical properties of the dye molecule [2]. If cyclization took place at the position vicinal to the nitro group (I), the absorption maximum for the dye would be much higher, as the absorption maximum of quinocarbocyanine prepared from an analogous salt containing an alkyl radical at the heterocyclic nitrogen atom is 630 mμ [3].

The symmetrical carbocyanine (III) was obtained by the condensation of the salt (II) with orthoformic ester [4].



The trimethine cyanines (IV; V) of unsymmetric structure were synthesized by the condensation of the N-m-

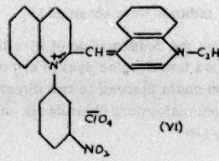
-nitrophenylquinaldinium salt with 2-β-acetanilidovinyltrimethylindolenine iodide and 2-β-acetanilidovinylbenzothiazole ethiodide [5], and these had absorption maxima of 579.5 and 590 mμ respectively in ethanol solution. In



(IV) (V)

these unsymmetrical molecules the nitro group in the meta position of the phenyl radical displaced the absorption maxima, in comparison with the analogs without nitro groups, by 7.5 mμ (IV) and 4 mμ (V).

The isocyanine (VI) [6] was also prepared from the quaternary salt and quinoline ethiodide.



(VI)

EXPERIMENTAL

N-m-Nitrophenylquinaldinium perchlorate (II). 4 g of m-nitrodiphenylamine, 4 ml of paraldehyde, 2 ml of concentrated hydrochloric acid, and 6 ml of dioxane were placed in a tube. The tube was sealed and heated 25 minutes on the boiling water bath. The condensation product was a semithick black mass. The contents of the tube were treated several times with ether, and then dissolved in ethyl alcohol. Aqueous potassium perchlorate solution was added to the alcohol solution till the formation of a light precipitate of a pale brown color ceased. The filtrate was evaporated to half its volume, and then another small amount of potassium perchlorate solution was added. The precipitate was filtered off, the solution evaporated till a scarcely visible oily film was formed, and left till the following day. The crystals which formed were filtered off, washed with water, and dried in the air. The result was yellow crystals, m.p. 230° (from aqueous alcohol).

Found %: Cl 9.50. $C_{16}H_{13}O_6N_2Cl$. Calculated %: Cl 9.71.

Bis-(1-m-nitrophenylquinoline-2)-trimethinecyanine perchlorate (III). 0.37 g of m-nitrophenylquinaldinium perchlorate, 0.3 ml of ethyl formate, and 3 ml of pyridine was placed in a small flask, which was then heated on an oil bath 50 minutes with gentle boiling and constant shaking of the reaction mixture. The mixture was then left till the following day. The dye was isolated from pyridine solution in the form of a dark green powder by treatment with ether and anhydrous alcohol. Crystallization from alcohol yielded a finely crystalline powder with a metallic luster. A solution in alcohol had an intense color. The yield after recrystallization was 0.134 g (42%). The substance melts above 300°.

Found %: Cl 5.38. $C_{33}H_{23}O_8N_4Cl$. Calculated %: Cl 5.55.

(1-m-Nitrophenylquinoline-2)-(1,3,3-trimethylindolenine-2)-trimethinecyanine perchlorate (IV). The dye was prepared by gently boiling 55 minutes under a reflux condenser a mixture consisting of 0.23 g of 2-β-acetanilidovinyl-3,3-dimethylindolenine methiodide, 0.21 g of the quaternary salt (II), and 4 ml of pyridine. The mixture was then left to crystallize till the following day. The precipitated dye was filtered off, washed with a small amount of alcohol and with ether, and crystallized from alcohol. It forms fine crystals with a bronze color. Yield 0.114 g (41%). M.p. 170-220° (decomp.).

Found %: Cl 6.77. $C_{29}H_{28}O_6N_3Cl$. Calculated %: Cl 6.46.

(1-m-Nitrophenylquinoline-2)-(3-ethylbenzothiazole-2)-trimethinecyanine perchlorate (V). 0.23 g of 2-β-

-acetanilidovinylbenzothiazole ethiodide, 0.21 g of the perchlorate of salt (II), and 3 ml of pyridine was heated 35 minutes under a reflux condenser. The dye was precipitated from the pyridine solution by water. The yield of dye after recrystallization from alcohol was 0.171 g (57%). M.p. 228-229° (decomp.).

Found %: Cl 6.22. $C_{27}H_{22}O_6N_3Cl$. Calculated %: Cl 6.41.

(1-m-Nitrophenylquinoline-2)-(1-ethylquinoline-4)-monomethinecyanine perchlorate (VI). 0.18 g of the quaternary salt (II), 0.14 g of quinoline ethiodide, and 4 ml of alcoholic alkali was heated 50 minutes on the oil bath, after which the mixture was left till the following day. Recrystallization from aqueous alcohol yielded 0.105 g (42%) of small crystals with a copper luster. M.p. 218-220° (decomp.). Absorption maximum 556 mμ.

Found %: Cl 6.48. $C_{27}H_{22}O_6N_3Cl$. Calculated %: Cl 6.81.

SUMMARY

1. The reaction of the cyclization of m-nitrodiphenylamine into N-aryl-quinaldinium derivatives was studied; a quaternary salt not described in the literature—N-m-nitrophenylquinaldinium perchlorate—was synthesized.

2. This salt was used in the preparation of 4 new cyanine dyes of symmetric and asymmetric structure.

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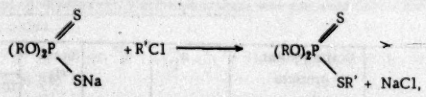
* T.p. = C. B. Translation pagination

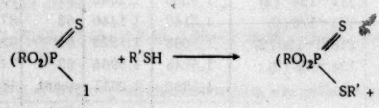
THE REACTION OF DIALKYLDITHIOPHOSPHATES WITH ETHYLENE OXIDE

M. I. Kabachnik, T. A. Mastryukova and V. N. Odnoralova

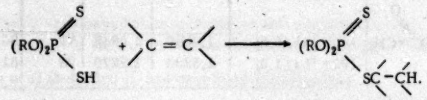
The known methods for the synthesis of substituted esters of dithiophosphoric acid are based on the reaction between O,O-dialkyldithiophosphate salts and halogen derivatives [1]:



or on the reaction of dialkylchlorothionophosphates with mercaptans or mercaptides [1b, 2]



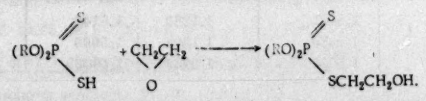
Substituted esters of dithiophosphoric acid are also formed by the addition of free O,O-dialkyldithiophosphates to various unsaturated compounds [3].



Since dialkyldithiophosphates are nucleophilic reagents, they add on readily to unsaturated compounds containing activated double bonds, such as α,β-unsaturated acids and ketones, acrylonitrile, and similar compounds.

Ethylene oxide is known as a substance which readily adds on nucleophilic reagents. In addition to such reagents of this type as ammonia, amines, alcohols, carboxylic acids, and similar substances, ethylene oxide adds on to thiocarboxylic acids [4]:

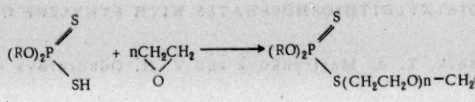
This gave reason to suppose that dialkyldithiophosphates should also add on ethylene oxide just as easily to form β-hydroxy substituted esters of dithiophosphoric acid:



On the other hand, dialkyldithiophosphates, being strong acids, might cause polymerization of ethylene oxide.

Our experiments showed that the addition reaction between dialkyldithiophosphates and ethylene oxide proceeds very easily. When the equivalent amount of ethylene oxide is passed through a dialkyldithiophosphate the temperature rises a little, and after the reaction product is held under reduced pressure it can be distilled under vacuum with little decomposition. The yields of the redistilled addition compounds are 60-65%. Table 1 shows the physical constants of the O,O-dialkyl- β-hydroxyethyldithiophosphates obtained.

When ethylene oxide is passed rapidly through a dialkyldithiophosphate, considerable heat is evolved and a colorless viscous substance which cannot be distilled under vacuum is formed. It seems likely that the reaction proceeds with the formation of ethylene oxide polymerization products:



The β-hydroxyethyl esters of O,O-dialkyldithiophosphoric acids obtained are viscous liquids readily soluble in organic solvents and insoluble in water.

TABLE 1

Serial No.	Formula	Boiling point, at pressure (mm)	n_D^{20}	d_4^{20}	Yield (%)	MR_D found	MR_D calculated*
1	$(C_2H_5O)_2PSSCH_2CH_2OH$	119–120° (2)	1.5250	1.2042	65	58.50	58.26
2	$(C_3H_7O)_2PSSCH_2CH_2OH$	124–126 (2)	1.5140	1.1440	62	67.99	67.54
3	$(iso\text{-}C_3H_7O)_2PSSCH_2CH_2OH$	118.5–120 (2)	1.5083	1.1323	59	68.04	67.54
4	$(iso\text{-}C_4H_9O)_2PSSCH_2CH_2OH$	135–138 (2)	1.5045	1.0965	63	77.40	76.77
5	$(CH_3O)_2PSSCH_2CH_2OH$	–	1.5380	1.2911	quant.	48.99	49.06
6	$(C_2H_5O)_2PSSCH_2CH_2OC(=O)-CH_3$	135.5–136.5 (1.5)	1.5010	1.1845	70	67.72	67.66
7	$(iso\text{-}C_4H_9O)_2PSSCH_2CH_2OC(=O)-CH_3$	140–141 (0.5)	1.4890	1.0948	71	86.58	86.14
8	$(C_2H_5O)_2PSSCH_2CH_2Cl$	103–104 (1.5)	1.5230	1.2270	23	61.93	61.64

* The group refractivity for two sulfur atoms was taken as 18.72 [5].

The addition of ethylene oxide to dialkyldithiophosphates is undoubtedly quantitative. This can be seen from the fact that the crude reaction mixture formed in the absorption of 1 mole of ethylene oxide by 1 mole of an O,O-dialkyldithiophosphate agrees almost exactly in its refractive index and specific gravity with the pure O,O-dialkyl-β-hydroxyethyldithiophosphates, as Table 2 shows.

TABLE 2

Formula	Crude product		Pure substance	
	n_D^{20}	d_4^{20}	n_D^{20}	d_4^{20}
$(C_3H_7O)_2PSSCH_2CH_2OH$	1.5121	1.1383	1.5140	1.1440
$(iso\text{-}C_3H_7O)_2PSSCH_2CH_2OH$	1.5080	1.1304	1.5083	1.1323
$(iso\text{-}C_4H_9O)_2PSSCH_2CH_2OH$	1.5030	1.0933	1.5045	1.0965

O,O-Dialkyl-β-hydroxyethyldithiophosphates are oxidized relatively easily by nitric acid. They are decomposed by dilute alkali. Acetic anhydride acetylates their hydroxyl groups and the corresponding acetyl derivatives are formed. Their physical constants are shown in Table 1. Phosphorus pentachloride substitutes the hydroxyl group of O,O-diethyl-β-hydroxyethyldithiophosphate with the formation of O,O-diethyl-β-chloroethyldithiophosphate. There is a patent reference for the synthesis of this last substance by another method, but its constants are not given [6].

EXPERIMENTAL

The O,O-dialkyldithiophosphates were prepared by a method described by us previously [7].

The reaction of ethylene oxide with dialkyldithiophosphates.

Thoroughly purified and dried ethylene oxide was passed into the dialkyldithiophosphate until the increase in weight was close to the theoretical value. The reaction temperature was kept at 30° by cooling the reaction mixture and by regulation of the supply rate of ethylene oxide. The end of the reaction was determined by the absence of an acid reaction to litmus. Excess ethylene oxide was then removed and the residue was distilled under vacuum in the presence of 0.1-0.2 g of benzidine.

O,O-Diethyl-β-hydroxyethyldithiophosphate was prepared from 7.4 g of O,O-diethyldithiophosphate and 2.5 g of ethylene oxide.

Found%: C 31.24, 31.15; H 6.57, 6.67; P 13.13, 13.44; S 27.44, 27.68. $C_6H_{15}O_3PS_2$. Calculated %: C 31.29 H 6.54; P 13.45; S 27.85.

O,O-Dipropyl-β-hydroxyethyldithiophosphate was prepared from 10.85 g of O,O-dipropyldithiophosphate and 2.75 g of ethylene oxide.

Found%: C 37.36, 37.30; H 7.54, 7.46; P 11.74, 11.99; S 24.64, 24.47. $C_8H_{19}O_3PS_2$. Calculated %: C 37.19 H 7.41; P 11.99; S 24.82.

O,O-Diisopropyl-β-hydroxyethyldithiophosphate was prepared from 7.74 g of O,O-diisopropyldithiophosphate and 1.63 g of ethylene oxide.

Found%: C 37.43, 37.33; H 7.56, 7.56; P 12.28, 12.41; S 24.55, 24.52. $C_8H_{19}O_3PS_2$. Calculated %: C 37.19 H 7.41; P 11.99; S 24.82.

O,O-Diisobutyl-β-hydroxyethyldithiophosphate was prepared from 9.68 g of O,O-diisobutyldithiophosphate and 2.25 g of ethylene oxide.

Found %: C 41.79, 41.95; H 7.94, 8.13; P 10.70, 10.74; S 22.51, 22.13. $C_{10}H_{23}O_3PS_2$. Calculated %: C 41.94 H 8.09; P 10.82; S 22.39.

O,O-Dimethyl-β-hydroxyethyldithiophosphate was prepared from 8.1 g of O,O-dimethyldithiophosphate and 2.95 g of ethylene oxide. In view of its thermal instability the product could not be distilled under vacuum.

Acetylation of O,O-dialkyl-β-hydroxyethyldithiophosphates.

To a solution of the dialkyl-β-hydroxyethyldithiophosphate in dry pyridine acetic anhydride was slowly added dropwise in such a manner that the temperature did not rise above 28-30°. The reaction mass was then heated 1.5 hours at 40-50° and left overnight. It was then decomposed by 5% acetic acid with cooling, the oil which formed was separated off, and the aqueous layer was extracted with ether. The combined extracts were washed with dilute acetic acid, 5% soda solution, and water. The ether extract was dried and distilled under vacuum.

O,O-Diethyl-β-acetoxyethyldithiophosphate was prepared from 5.5 g of undistilled diethyl-β-hydroxyethyldithiophosphate and 2.9 g of acetic anhydride in 5 ml of pyridine.

Found%: C 35.37, 35.31; H 6.52, 6.36; P 11.19, 11.44; S 23.52, 23.58. $C_8H_{17}O_4PS_2$. Calculated %: C 35.28; H 6.29; P 11.38; S 23.55.

O,O-Diisobutyl-β-acetoxyethyldithiophosphate was prepared from 11.65 g of diisobutyl-β-hydroxyethyldithiophosphate and 5.9 g of acetic anhydride dissolved in 10 ml of pyridine.

Found%: C 44.05, 44.17; H 7.67, 7.75; P 9.31, 9.09. $C_{12}H_{25}O_4PS_2$. Calculated% : C 43.89; H 7.67; P 9.44.

Preparation of O,O-diethyl-β-chloroethyldithiophosphate.

20 g of phosphorus pentachloride was added in small portions with stirring and cooling to 20 g of O,O-diethyl-β-hydroxyethyldithiophosphate in 60 ml of carbon tetrachloride. The reaction mixture was then stirred 1 hour at −2 to 0° and decomposed by ice-cold water. The reaction product was extracted with ether, washed with dilute soda solution and with water, dried over calcium chloride and distilled under vacuum. The yield was 5 g of O,O-diethyl-β-chloroethyldithiophosphate.

Found%: C 29.57, 29.43; H 5.33, 5.42; P 12.16, 12.40; Cl 14.37. $C_6H_{14}O_2PS_2Cl$. Calculated %: C 28.97; H 5.63; P 12.45; Cl 14.29.

SUMMARY

1. The reaction between ethylene oxide and dialkyldithiophosphates was investigated.

2. Several O,O-dialkyl-β-hydroxyethyldithiophosphates were prepared in 60-65% yields.

3. The presence of hydroxyl groups in O,O-dialkyl-β-hydroxyethyldithiophosphates was shown by acetylation and formation of a β-chloro derivative.

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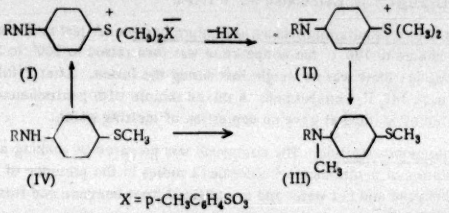
THE DIPOLAR IONS FORMED BY THE REMOVAL OF PROTONS FROM NH GROUPS

X. REGROUPING OF DIPOLAR IONS OF THE SULFONIUM SERIES

A. M. Simonov

It was established earlier that sulfonium salts containing an NH group combined with a picryl, 2,4-dinitrophenyl, or β-anthraquinonesulfonyl radical are easily converted into dipolar ions by the action of dilute alkali by the removal of a proton from the NH group [1]. In the present communication it is shown that this conversion also occurs if the mobility of the hydrogen in the NH group is due to the influence of a p-nitrobenzenesulfonyl or p-nitrobenzoyl radical attached to it.

Sulfonium salts (I) (R = p-$NO_2C_6H_4SO_2$, p-$NO_2C_6H_4CO$) can be easily converted into dipolar ions (II), which are brightly colored crystalline substances insoluble in nonpolar solvents.



X = p-$CH_3C_6H_4SO_3$

Fusion of the dipolar ions (II) results in the formation of pale colored melts which crystallize on cooling. The yellow crystalline substances so formed, in contrast to the original betaines, are insoluble in dilute acids and dissolve in nonpolar solvents. It was natural to suppose that the fusion of betaines (II) results in the regrouping described for the phenol betaines [2], amino acid betaines [3], and betaine carbeniates [4], which consists of displacement of the alkyl radical from the onium atom to the anionic center of the molecule; in that event the corresponding N-alkyl anilides (III) should be formed from the betaines (II). This was confirmed experimentally by the fact that the product formed by the fusion of a betaine (II) (R = p-nitrobenzenesulfonyl) proved identical with the p-thiomethoxy-N-methanilide of the p-nitrobenzenesulfonic acid (III) prepared by the methylation of the p-thiomethoxyanilide of the p-nitrobenzenesulfonic acid (IV).

In the regrouping of the dipolar ions (II), the alkyl radical removed from the sulfonium group interacts with the electron-donor center of the molecule and is therefore cationic in character.

D. N. Kursanov and V. N. Setkina [5] developed views on the mechanism of the exchange and decomposition reactions of tetrasubstituted ammonium salts, according to which these reactions proceed by a heterolytic mechanism, and consist of the interaction of electrophilically active groups split off from the onium atom with the electron-donor centers in the molecules of the onium salt or of substances reacting with it. Observations made in the course of the present work show that these concepts may be extended to analogous conversions of sulfonium salts.

EXPERIMENTAL

1. p-Nitrobenzenesulfonic acid 4-thiomethoxyanilide. This compound was prepared by the reaction between p-thioanisidine and p-nitrobenzene sulfonic chloride (1 mole) in pyridine. It forms pale yellow crystals (from alcohol), m.p. 165-165.5°, soluble in benzene and aqueous ammonia solution, insoluble in water.

Found %: S 19.73. $C_{13}H_{12}O_4N_2S_2$. Calculated %: S 19.77.

2. Dimethyl-[4-(p-nitrobenzenesulfamino)-phenyl]sulfonium p-toluenesulfonate. This compound was prepared by the fusion of p-nitrobenzenesulfonic acid 4-thiomethoxyanilide with the methyl ester of p-toluenesulfonic acid at 130-140° (1 hour). It forms colorless crystals (from methanol), soluble in water and alcohol. The melting point, which depends on the rate of heating, is about 180°.

Found %: S 18.83. $C_{21}H_{22}O_7N_2S_3$. Calculated %: S 18.84.

3. Dimethyl-[4-(p-nitrobenzenesulfamino)-phenyl]sulfonium betaine. A small excess of 2 N alkali or ammonia solution was added dropwise to a solution of 1.02 g of the quaternary salt (Experiment 2) in 20 ml of water at 75°. Brown crystals were precipitated, and these were washed with water and dried in a desiccator over caustic potash. The yield was 90%. The compound was crystallized from a large volume of alcohol in the form of pale brown shiny thin plates, insoluble in benzene and dioxane, fairly easily soluble in water on warming, and soluble with difficulty in pyridine. The compound does not become hydrated when left to stand in water vapor. The melting point depends on the rate of heating. At about 185° a not quite clear brown melt is formed, which becomes yellow and transparent as the result of reactions taking place in the melt when the temperature is raised a few degrees; yellow crystals form on cooling.

Found %: S 18.88, 18.83. $C_{14}H_{14}O_4N_2S_2$. Calculated %: S 18.95.

4. p-Nitrobenzenesulfonic acid 4-thiomethoxy-N-methylanilide. a) From p-nitrobenzenesulfonic acid 4-thiomethoxyanilide: The compound was prepared by the reaction between p-nitrobenzenesulfonic acid 4-thiomethoxyanilide in dilute caustic soda, and dimethyl sulfate. It forms pale yellow needles (from alcohol), m.p. 145.5°, soluble in benzene, and with difficulty in ether.

Found %: S 18.77, 18.84. $C_{14}H_{14}O_4N_2S_2$. Calculated %: S 18.95.

b) From dimethyl-[4-(p-nitrobenzenesulfamino)phenyl]sulfonium betaine. A test tube containing 0.2 g of the betaine was placed in an oil bath heated to 190°; the temperature was then raised to 200° in 3 minutes. The yellow clear melt soon crystallized on cooling; there was no weight loss during the fusion. After 2-fold crystallization from alcohol pale yellow crystals with m.p. 145.5° were formed. A mixed sample with p-nitrobenzenesulfonic acid 4-thiomethoxymethylanilide prepared by Method a) gave no depression of melting point.

5. p-Nitrobenzoic acid 4-thiomethoxyanilide. The compound was prepared by shaking an aqueous emulsion of p-thioanisidine with a benzene solution of p-nitrobenzoyl chloride (1 mole) in the presence of sodium bicarbonate. The precipitate was washed with benzene and hot water and crystallized from benzene and from alcohol. It forms thin pale yellow needles, m.p. 215-215.5°.

Found %: S 11.06. $C_{14}H_{12}O_3N_2S$. Calculated %: S 11.12.

6. Dimethyl-[4-(p-nitrobenzoylamino)-phenyl]sulfonium p-toluenesulfonate. Yellowish-white crystals (from 50% alcohol), m.p. 217-219°.

Found %: S 13.50. $C_{22}H_{22}O_6N_2S_2$. Calculated %: S 13.51.

7. Dimethyl-[4-(p-nitrobenzoylamino)-phenyl]sulfonium betaine. 2.5 ml of 2 N alkali solution was added dropwise to a solution of 0.95 g of the quaternary salt (Experiment 6) in 10 ml of 50% alcohol. The betaine, which was formed in almost quantitative yield as a brick-red precipitate, was crystallized from 70% alcohol. The compound is insoluble in benzene and dioxane, and dissolves with great difficulty in acetone, pyridine, and water. It melts at about 145° with the formation of a turbid brown melt which on further heating becomes yellow and clear. The betaine is not hydrated when left to stand in water vapor.

Found %: S 10.59, 10.58. $C_{15}H_{14}O_3N_2S$. Calculated %: S 10.61.

8. p-Nitrobenzoic acid 4-thio-N-methylanilide (from dimethyl-[4-(p-nitrobenzoylamino)-phenyl]sulfonium betaine). A test tube containing a weighed portion of the betaine was placed in oil heated to 145°, and the temperature was raised to 155° during 10 minutes. The yellow clear melt crystallized on cooling. It was broken up, washed with dilute acetic acid to remove residual betaine, and crystallized from dilute alcohol. It forms pale yellow crystals, m.p. 107-108° (in one of the experiment a bright yellow form with m.p. 87.5-88.5° was obtained).

Found %: S 10.59, 10.58. $C_{15}H_{14}O_3N_2S$. Calculated %: S 10.61.

SUMMARY

Dipolar ions of the structure (II) (R = p-nitrobenzenesulfonyl, p-nitrobenzoyl) which are formed by the action

of alkali on sulfonium salts (I), become regrouped into N-alkyl anilides on fusion.

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COMPLEX ARYLLITHIUM COMPOUNDS

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It was shown in our earlier papers that aromatic lithium compounds obtained in ether medium are complex compounds [1] containing ether, and it was also found that aryllithium compounds are capable of forming complexes with dioxane and tertiary amines [2].

In continuation of the investigations of complex formation by organic compounds of alkali metals, we studied 9-fluorenyllithium and 3-pyrenyllithium, previously used in synthesis without isolation in the free state.

9-Fluorenyllithium was prepared by the action of n-butyllithium on fluorene in ether-benzene solution. The solvent was removed from the crystalline product under vacuum at room temperature. When steady loss of weight was reached, the compound was analyzed for metal and hydrocarbon content. The analysis showed that the compound contains 2 molecules of diethyl ether. The dietherate of 9-fluorenyllithium when kept under vacuum at room temperature gradually loses the complex-bound ether and after several hours becomes the monoetherate.

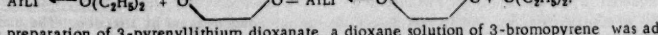
3-Pyrenyllithium was prepared by the double decomposition reaction between 3-bromopyrene and n-butyllithium in ether-benzene medium. It was found that it contains one molecule of ether for each molecule of the metalorganic compound, combined more stably with the metal than in 9-fluorenyllithium.

Dioxane complexes of 9-fluorenyllithium and 3-pyrenyllithium were prepared by the action of a benzene solution of n-butyllithium on a benzene-dioxane solution of fluorene or 3-bromopyrene. The dioxane complexes were analyzed for lithium, hydrocarbon, and dioxane contents. The dioxane was determined by means of our technique in the form of a molecular compound with mercuric chloride, with which good analytical results could be obtained after the introduction of a correction for the solubility of the molecular compound in water. The use of this technique showed that in the above conditions 9-fluorenyllithium is obtained as a complex compound with one molecule of dioxane.

Investigation of 3-pyrenyllithium showed that it also contains 1 molecule of dioxane, but that, in addition, it apparently contains 1 molecule of benzene per 2 molecules of the metalorganic compound. This unexpected observation led us to verify the composition of the previously described dioxane complexes [2], which were also prepared in the presence of benzene, and the investigation of which was in some instances difficult because of their low stability.

Quantitative determinations of dioxane showed that the previously described dioxane compounds of lithium-aromatic compounds of the benzene series, and also of α-naphthyllithium when prepared in a benzene-dioxane medium contain not 2 but 1 molecule of dioxane, but in addition their composition apparently includes 1 molecule of benzene per 2 molecules of the aryllithium, which is held less firmly than the dioxane, and which in the case of α-naphthyllithium splits off completely with relative ease.

Dioxane complexes free from benzene may be prepared by carrying out the reactions in ether medium in the presence of dioxane. Phenyllithium dioxanate was prepared by the addition of dioxane to an ether solution of phenyllithium, obtained by the Woods and Gilman reaction between triphenylantimony and n-butyllithium [3]. The dioxane complex of α-naphthyllithium was prepared by the action of dioxane on α-naphthyllithium etherate, obtained from α-bromonaphthalene and n-butyllithium. In both cases dioxane complexes are formed by a displacement reaction. Dioxane, as the stronger complex-former, displaces ether from its aryllithium compounds:



For the preparation of 3-pyrenyllithium dioxanate, a dioxane solution of 3-bromopyrene was added to an ether solution of n-butyllithium; this resulted in the formation of a complex containing 3 molecules of dioxane with 2 molecules of 3-pyrenyllithium.

We have shown that alkyllithium compounds can form complex compounds with dioxane. These compounds

are unstable. For example, n-butyllithium dioxanate may be isolated in the crystalline state at about −10°. It decomposes at higher temperatures with evolution of gaseous products.

Talalaeva and Kocheshkov [4] have commented on our studies of aryllithium complexes. They refer to the generally known fact[5] that in the double decomposition reaction between aryl bromides and n-butyllithium, which we used for the preparation of aryllithium complexes, lithium bromide is formed as a side product. In their words, "the presence of lithium halide impurity may significantly change" our data on the composition of the etherates and other aryllithium complexes. In confirmation, these authors point out that when phenyllithium is prepared from bromobenzene and lithium, it contains lithium bromide when separated from solution.

We must point out that in reality only traces of lithium bromide are present in the ether and other complexes of α-napthyllithium, 9-phenanthryllithium, and the other aryllithium compounds obtained by us by means of the above reaction. As regards phenyllithium etherate, we take this opportunity to present data on this compound in greater detail.

Phenyllithium etherate, when prepared from bromobenzene and lithium, does contain a considerable amount of lithium bromide. However, its content does not in any way correspond to a complex with the composition $2C_6H_5Li \cdot 2(C_2H_5)_2O \cdot LiBr$, as is held by Talalaeva and Kocheshkov [4]. In reality the lithium halide content approximately corresponds to the above composition (21.56%) only if isolation of the complex is limited to removal of the mother liquor from it by suction. If, however, the filtered precipitate is rapidly washed with a small volume of very cold ether (cooled to −70 to −100°), then the lithium bromide content is found to be less by 5-6% (about 16-17%). Even in this instance, however the precipitate formed is not a homogeneous substance. If it is treated at room temperature with a small quantity of ether, with a small portion left undissolved, it is found that the undissolved portion contains more lithium bromide (21-23%) than the dissolved portion (14-15%). Thus there is no doubt that the crystallization of phenyllithium from ether solution is accompanied by the separation of lithium bromide which contaminates the etherate. It is not possible to remove this impurity by means of ether, as lithium bromide is easily soluble in ether and partly dissolves during treatment of the precipitate with ether. To separate the lithium bromide impurity it is, however, possible to use pentane (or isopentane or benzene) in which lithium bromide is not soluble, while phenyllithium etherate dissolves readily. When a mixture of phenyllithium etherate and lithium bromide is treated with pentane, most of the complex is dissolved, while about a half of the precipitate which remains on the filter consists of lithium bromide. The pentane-washed complex, the amount of which is determined from the difference between the weight of the original precipitate and the residue on the filter, contains 3.45-3.57% lithium and 9.26-9.42% lithium bromide. These contents of lithium and lithium bromide correspond to a compound consisting of 5 molecules of phenyllithium, 6 molecules of ether, and 1 molecule of lithium bromide ($5C_6H_5Li \cdot 6(C_2H_5)_2O \cdot LiBr$).

It is difficult to decide definitely whether the lithium bromide is really a component of the complex or an impurity but, although lithium bromide is insoluble in pure pentane the possibilty is not excluded that it is soluble in pentane containing phenyllithium etherate, and therefore it may enter the filtrate. It is probable, however, that the lithium bromide, about 9% of which is found in phenyllithium etherate, is a constituent part of the complex. We are led to this conclusion by indirect considerations, namely by the fact that phenyllithium etherate containing lithium bromide is very much more stable than phenyllithium etherate formed in absence of lithium bromide.

EXPERIMENTAL

All the operations were performed in a nitrogen atmosphere. Double-horned ampoules were used as reaction vessels. The complexes were isolated in a special funnel with a glass filter (No. 2) described previously [1].

9-Fluorenyllithium diethetate. To a benzene solution of n-butyllithium (20 ml, containing 0.024 mole) cooled in ice, 2 g of fluorene (0.012 mole) dissolved in a mixture of 9 ml of benzene and 4 ml of ether was slowly added with shaking. The yellow precipitate was washed with 60 ml of benzene and dried in vacuum (at 2-3 mm Hg) 1 hour to constant loss of weight (0.1% loss in 5 minutes). Anhydrous ether was then added to the funnel, and the complex was decomposed by a solution of methanol in ether. The ether layer was washed with water, separated from the aqueous layer, and the ether was distilled off. The residue, which was fluorene, was dried in a vacuum desiccator to constant weight. Alkali was determined in the aqueous layer by titration. The difference between the weight of the complex and the sum of the weights of lithium and hydrocarbon gave the weight of the ether bound in the complex. In the experiment 2.7620 g of complex was obtained, containing 0.0604 g of lithium and 1.4390 g of fluorenyl.

Found %: Li 2.18; fluorenyl 52.01. $C_{13}H_5Li \cdot 2(C_2H_5)_2O$. Calculated %: Li 2.17; fluorenyl 51.56.

3-Pyrenyllithium etherate. An ether solution of n-butyllithium, prepared from 0.25 g of lithium, 2.4 g of n-butyl chloride, and 10 ml of ether, was filtered to remove lithium chloride, diluted with 10 ml of ether, and cooled with ice-cold water. 3 g of 3-bromopyrene, dissolved in 10 ml of benzene, was added to the solution gradually with shaking. The yellow precipitate was filtered off, washed with 20 ml of ether, and dried 35 minutes to constant loss of weight (0.03% in 5 minutes).

The analysis was performed as described above. 1.9164 g of substance was obtained, containing 0.0460 g of lithium and 1.3570 g of pyrenyl.

Found %: Li 2.40; pyrenyl 70.81. $C_{16}H_9Li \cdot (C_2H_5)_2O$. Calculated %: Li 2.46; pyrenyl 71.28.

The complex contained 0.55% of lithium bromide.

Method for the analysis of dioxanates of aryllithium compounds. Dioxane was quantitatively determined in the aryllithium compounds in the form of a molecular compound with mercuric chloride, which is sparingly soluble in water [6]. It was previously established by the use of synthetic mixtures that in definite conditions 81-83% of the mercuric chloride dioxanate taken for the experiment is separated from the aqueous solution.

The analysis of the dioxane complexes was carried out as follows. The metalorganic compound prepared for the analysis in the analytical funnel described previously [1] was covered with 10 ml of anhydrous ether and, with cooling, carefully hydrolyzed by methanol added periodically dropwise through the upper tap E. 10 ml of water was then added, the mixture was shaken, and the aqueous and ether layers forced out through the lower opening into a separating funnel. The analytical funnel was rinsed with 7 ml of water and 5 ml of ether, and the solvents were transferred to the same separating funnel. (If the hydrocarbon formed during hydrolysis remained undissolved in the stated amount of ether, as for example anthracene, it was dissolved in hot benzene for quantitative determination; see below). The ether layer was separated from the aqueous layer in the separating funnel, and washed with 8 ml of water. Dioxane, lithium, and lithium bromide were determined in the aqueous layer, 25 ml of volume.

For this purpose 5 ml of the aqueous solution was first titrated to determine the alkali content, and then, after neutralization, the lithium bromide content was determined (by Mohr's method).

The remaining solution (20 ml) was neutralized with 1.0 N sulfuric acid solution, hot aqueous mercuric chloride solution (2 g in 5 ml of water) was added, and the liquid cooled in ice during 2 hours. The mercuric chloride dioxanate formed was filtered off, dried overnight in a vacuum desiccator, and weighed. As a small amount of dioxane remained in the ether layer, a solution of 0.3 g of mercuric chloride in 5 ml of water was added to the latter, the liquid was shaken, the ether distilled off, 5 ml of benzene added, and the layers separated. The aqueous layer was cooled, and the mercuric chloride dioxanate was filtered off, dried, and weighed.

The amount of dioxane was calculated from the total amount of mercuric chloride dioxanate, with allowance for the fact that $^1/_5$ of the aqueous solution was used for determination of alkali. For the determination of the percentage dioxane content in the metalorganic compound a correction is introduced based on the fact that 83% of the dioxane contained in the complex is determined by this method.

For determination of the hydrocarbon content, the solvent was removed from the benzene solutions and the residue dried in a vacuum desiccator *.

9-Fluorenyllithium dioxanate. 2 g of fluorene was dissolved in a mixture of 4 ml of benzene and 4 ml of dioxane. The solution was cooled in ice and added dropwise to a 1.22 N solution of n-butyllithium in benzene (10 ml) also cooled in ice. A yellow precipitate of dioxanate was immediately formed; this was filtered off, washed with benzene, and dried 70 minutes to constant weight. 2.2220 g of the complex was obtained, containing 0.0562 g of lithium, 1.4180 g of fluorenyl, and 0.7402 g of dioxane.

Found %: Li 2.53; fluorenyl 63.83; dioxane 33.31. $C_{13}H_9Li \cdot C_4H_8O_2$. Calculated %: Li 2.66; fluorenyl 63.61; dioxane 33.73.

3-Pyrenyllithium dioxanate. A filtered solution of n-butyllithium in ether, prepared from 0.25 g of lithium, 2.1 ml of n-butyl chloride, and 10 ml of ether, was diluted with 20 ml of ether. To the cooled solution 2.5 g of 3-bromopyrene dissolved in 8 ml of anhydrous dioxane was added slowly with shaking. The pale yellow precipitate was filtered off, washed with 2 lots of 10 ml of ether, and dried 50 minutes to constant loss of weight (0.1% in 5 minutes).

* For naphthalene determination the drying was continued 1 hour.

2.0462 g of the complex was obtained, containing 0.0416 g of lithium, 1.1790 g of pyrenyl, and 0.7884 g of dioxane.

Found %: Li 2.03; pyrenyl 57.62; dioxane 38.59. $2C_{16}H_9Li \cdot 3C_4H_8O_2$. Calculated %: Li 2.04; pyrenyl 59.10; dioxane 38.84.

0.2% of lithium bromide was found in the complex.

Phenyllithium dioxanate. The phenyllithium required for the preparation of the dioxanate was prepared by means of the Woods and Gilman reaction between triphenylantimony and n-butyllithium [3].

A solution of 2.5 g of triphenylantimony in 5 ml of benzene was added to 11.5 ml of benzene solution of n-butyllithium (1.22 N). The reaction mass was heated 3 hours at 80-85°, the phenyllithium which separated out was filtered off, washed with hexane, and dried under vacuum. The phenyllithium was then dissolved in 10 ml of ether, the solution was filtered, and a mixture of 2 ml of dioxane and 5 ml of ether was added. A colorless crystalline precipitate was instantly formed. After 10 minutes the precipitate was filtered off, washed with 10 ml of ether, and dried under vacuum 15 minutes to constant weight.

0.9160 g of the complex was obtained, containing 0.0394 g of lithium and 0.4600 g of dioxane.

Found %: Li 4.30; dioxane 50.22. $C_6H_5Li \cdot C_4H_8O_2$. Calculated %: Li 4.03; dioxane 51.22.

α-Naphthyllithium dioxanate. A filtered solution of n-butyllithium in ether, prepared from 0.4 g of lithium, 2.5 ml of n-butyl chloride, and 15 ml of anhydrous ether, was diluted with 60 ml of ether. The solution was cooled in ice, and 2.4 ml of α-bromonaphthalene diluted with 10 ml of ether was gradually added.

To the resultant solution of α-naphthyllithium 5 ml of dioxane diluted with 5 ml of ether was slowly added. α-Naphthyllithium dioxanate began to separate out on the addition of the first few drops of dioxane. After 1 hour the precipitate was filtered off and washed with 20 ml of ether. It was dried under vacuum 25 minutes to constant loss in weight (0.02% in 5 minutes).

2.6040 g of the complex was obtained, containing 0.0766 g of lithium, 1.4222 g of naphthyl, and 0.0416 g of dioxane.

Found %: Li 2.95; naphthyl 54.60; dioxane 40.00. $C_{10}H_7Li \cdot C_4H_8O_2$. Calculated %: Li 3.15; naphthyl 57.20; dioxane 39.67.

The complex contained 0.5% of lithium bromide.

SUMMARY

9-Fluorenyllithium and 3-pyrenyllithium form complex compounds with ether and dioxane.

Dioxanates of aryllithium compounds are formed by the action of dioxane on ether solutions of their etherates.

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STUDY OF THE SULFONATION REACTION

XXXVII. EQUILIBRIUM BETWEEN SODIUM SULFONATE, SULFONIC ACID, AND ITS ACID CHLORIDE

A. A. Spryskov and N. V. Aparyeva

Earlier we described [1] the conversion of sodium salts of some sulfonic acids of the aromatic series into their acid chlorides by the action of chlorosulfonic acid. Literature data on the subject were also cited. At the same time one of the present authors jointly with Yu. L. Kuzmina [2] studied the equilibrium between sulfonic acids and their acid chlorides in a medium consisting of chlorosulfonic acid and sulfuric acid. In the present investigation an attempt was made to study the equilibrium between p-dichlorobenzenesulfonic acid, its sodium salt, and the acid chloride, also in a medium consisting of various amounts of chlorosulfonic and sulfuric acids.

EXPERIMENTAL

Sodium 2,5-dichlorobenzenesulfonate was dissolved in a mixture of chlorosulfonic and sulfuric acids. The solution was poured into several vessels with ground glass stoppers and kept during various time intervals in a desiccator over phosphoric anhydride at room temperature (about 20°). The solutions were then poured onto ice, and the acid chloride which separated was filtered off, washed, dried and weighed.

If for every 2 moles of sodium sulfonate m moles of chlorosulfonic acid and n moles of sulfuric acid are added to the mixture, then, after equilibrium is attained according to the equation:

$$\underset{2-x}{2RSO_3Na} + \underset{m-x}{HSO_3Cl} + \underset{n-y}{H_2SO_4} \rightleftharpoons \underset{x}{RSO_2Cl} + \underset{y}{RSO_3H} + \underset{x+y}{2NaHSO_4}, \qquad (I)$$

the equilibrium constant will be given by the equation:

$$K = \frac{xy(x+y)^2}{(2-x-y)^2(m-x)(n-y)}. \qquad (II)$$

To find K, we add to both sides of Equation (I) 1 mole each of RSO_2Cl and HSO_3Cl and divide it into two equilibrium equations:

$$RSO_2Cl + H_2SO_4 \rightleftharpoons RSO_3H + HSO_3Cl \qquad (III)$$

$$2RSO_3Na + 2HSO_3Cl \rightleftharpoons 2RSO_2Cl + 2NaHSO_4.$$

With the notation used, the constant for the first equilibrium will be:

$$K_1 = \frac{y(m-x)}{x(n-y)}. \qquad (IV)$$

Its value was determined previously [2b] from experimental data for the equilibrium between p-dichlorobenzenesulfonic acid and its acid chloride, and was found to be 0.64. The amount x of acid chloride in the equilibrium system is found experimentally, and the amount y of the sulfonic acid is found from Equation (IV):

$$y = \frac{K_1 \cdot xn}{(m-x) + K_1 x}. \qquad (V)$$

Thus, K may be calculated with the aid of Formula (II). The experimental results shown in Table 1 give the values of the equilibrium constant K. The yield of acid chloride varies between 57.7 and 84%.

The time in which a state close to equilibrium is attained depends on the ratio of the amounts of chlorosulfonic and sulfuric acids. For example, if this ratio is about 25 (Experiment 19, Table 1) then for a state close to equilibrium to be reached it is sufficient to hold the mixture about 20 hours, while if the ratio is 2.2, not less than 150

hours is needed (Experiment 12), and for a ratio of 1.3, 1500 hours (Experiment 20).

By solving Equation (II) for x with the use of the mean value of K found, it is possible to calculate the yield of chloride for known values of m and n. A graphical method for solving this equation was chosen. To plot the graphical relationship, we equate the right hand side of Equation (II) to a certain value Q:

$$Q = \frac{xy(x+y)^2}{(2-x-y)^2(m-x)(n-y)}. \qquad (VI)$$

We take a number of values: $x = 1.4, 1.45, 1.5, 1.55, 1.6, 1.65$. For each value of x we calculated the value of y from Formula (V). By substitution of the values of x and y in Equation (VI) we find the values of Q and plot them on a graph against the corresponding values of x (see figure). Then from the ordinate corresponding to $K = 0.33$ we find the required value of x along the abscissa axis.

TABLE 1

Equilibrium State Between 2,5-Dichlorobenzenesulfonic Acid, Its Sodium Salts, and the Acid Chloride at 20°.

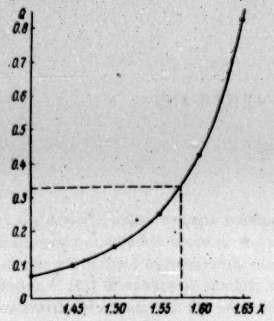
Experiment No.	Moles taken per 2 moles of sulfonate		Ratio m:n	Duration (hours)	Acid chloride formed, x moles per 2 moles of sulfonate	Equilibrium constant K
	HSO_3Cl m	H_2SO_4 n				
19	16.16	0.654	24.7	21	1.680	0.34
				34	1.678	
				47	1.682	
18	15.01	1.078	14.0	21	1.496	0.24
				49	1.524	
				73	1.590	
10	16.16	2.454	6.6	46	1.574	0.31
				70	1.572	
17	16.04	4.38	3.7	24	1.466	0.27
				34	1.468	
13	14.92	4.02	3.7	72	1.510	0.44
				144	1.494	
				240	1.496	
12	12.96	5.92	2.2	101	1.224	0.22
				151	1.292	
				219	1.260	
20	9.84	7.38	1.3	1368	1.100	0.47
				4822	1.054	

Mean : K = 0.33.

Table 2 shows the values for the acid chloride calculated by the method described and the experimental values for a state close to equilibrium.

Table 2 shows that the deviations between the calculated and experimentally determined amounts of acid chloride in the equilibrium mixture do not exceed 2%.

For the preparation of pure sodium 2,5-dichlorobenzenesulfonate, 2,5-dichlorobenzenechlorosulfonate with m.p. 37.5-38° was saponified by 50% alcohol and the solution was evaporated to dryness. The sulfonic acid formed was neutralized by alkali, and the salt was crystallized after evaporation and cooling the solution. The chlorosulfonic was distilled and analyzed as described previously [1b].



Graph for the function Q for Experiment No. 10 (Table 1).

TABLE 2

Equilibrium Between p-Dichlorobenzenesulfonic Acid, Its Sodium Salt, and the Acid Chloride

Experiment No.	Acid chloride in mixture (% of theoretical)		Deviation (%)
	Found	Calculated	
19	84.1	84.0	−0.1
18	79.5	81.5	+2.0
10	78.6	79.0	+0.4
17	73.4	74.0	+0.6
13	74.8	73.5	−1.3
12	64.6	65.8	+1.2
20	57.7	56.8	−0.9

SUMMARY

A study was made of the equilibrium between 2,5-dichlorobenzenesulfonic acid, its sodium salt, and the acid chloride in a medium consisting of sulfuric and chlorosulfonic acids at a temperature of about 20°. The equilibrium constant was found to be 0.33. The composition of the equilibrium mixture may be calculated by a graphical method with 1-2% accuracy. The reaction rate for the conversion of sulfonate into the chloride and the acid depends on the ratio of the chlorosulfonic and sulfuric acids. The reaction is much more rapid with a relatively high content of chlorosulfonic acid.

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THE ETHYL ESTER OF α-HYDROXYISOBUTYRIC ACID

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We describe below a single method for the preparation of the ethyl ether of α-hydroxyisobutyric acid directly from acetone cyanohydrin based on the use of the Pinner reaction [1], which does not require the isolation of the intermediately formed hydrochloride of α-hydroxyisobutyric acid imino ether; acetone cyanohydrin is heated with a solution of HCl in anhydrous alcohol, the reaction mixture is boiled with the calculated amount of water and, after neutralization of excess HCl the ethyl ester of α-hydroxyisobutyric acid is isolated by distillation; the yield is about 80 %. The methyl ester of α-hydroxyisobutyric acid may be synthesized by the same method.

EXPERIMENTAL

439 g of 26% solution of HCl in anhydrous alcohol was placed in a three-necked flask, 1.5 liters in capacity fitted with dropping funnel, stirrer, and a reflux condenser protected by a tube with calcium chloride, and 205 g (2.41 moles) of acetone cyanohydrin, b.p. 82-85° at 23 mm, was added with stirring. About one half of the total amount of acetone was added at once, and the rest in such a manner that the temperature of the solution did not rise above 50°. At the end of the addition of acetone cyanohydrin the solution was heated to 70°, the heating was stopped, and the solution left till the following morning. 43.4 ml (2.41 moles) of water was then added, the solution boiled 4 hours, and the reaction mixture neutralized at 0-10° by addition of ~ 20% NH_3 solution in anhydrous alcohol till neutral to congo. The ammonium chloride formed was separated off and washed in two stages with 100 ml of anhydrous alcohol; the combined filtrates were distilled with the aid of a plate-type column. The first fraction collected in the range 77-83°, weighed 190-200 g and contained about 3% of the ester; the second fraction, b.p. 42-49° at 135 mm, weighed about 100 g and contained 10-15% of the ester; the third fraction, b.p. 43-55° at 22-27 mm, 250 g in weight, was 95-98% ethyl ester of α-hydroxyisobutyric acid.

The pure ester is a colorless liquid with a fairly pleasant odor reminiscent of black currants. B.p. 50° at 17 mm, 60° at 28 mm, and 150° at atmospheric pressure.

From the residue after distillation, ~25 g of α-hydroxyisobutyric acid, m.p. 76-78°, was extracted after extraction of the residue with hot benzene and removal of most of the solvent.

In the preparation of the ester, ethyl chloride is formed as a side product when the reaction mixture is boiled. This can be collected by fitting to the reflux condenser of the apparatus in which the reaction is performed a downward spiral condenser and receiver cooled in a mixture of ice and salt. The amount of ethyl chloride obtained was 25-29 g.

SUMMARY

A description is given of the synthesis of the ethyl ester of α-hydroxyisobutyric acid from acetone cyanohydrin, based on the Pinner reaction.

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SYNTHESIS OF SUBSTITUTED DIPHENYL ETHERS

I. N. Gorbacheva, E. N. Tsvetkov, L. P. Varnakova, K. M. Losev and N. A. Preobrazhensky

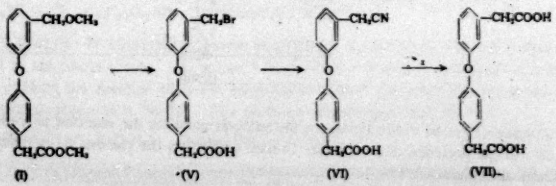
Diphenyl ethers lie at the basis of the structure of a large group of isoquinoline alkaloids, known as the bisco-claurine alkaloids (magnoline [1], dauricine [2], D-tubocurarine chloride [3] and others).

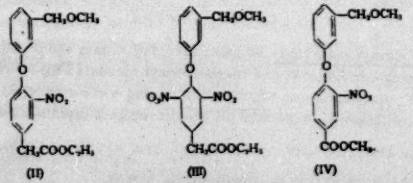
Numerous attempts to synthesize these complex ether-like bisbenzylisoquinoline compounds gave no conclusive results.

One of the methods for the synthesis is the reaction between the corresponding phenylethylamine and the dicarboxylic acid derived from the diphenyl ether, followed by cyclization of the resultant amide and formation of an isoquinoline base. The most involved stage of this scheme is the preparation of diphenyl ethers with definite substituent groups. The main synthesis method for diphenyl ethers is the reaction between potassium or sodium phenates and halogenated aromatic hydrocarbons. The reaction conditions and yields depend on the presence of substituents in the nuclei of both components.

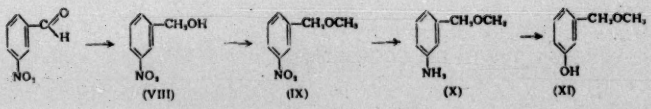
In view of the possibility of raising the mobility of the halogen by the influence of various groups, we prepared a series of diphenyl ethers containing substituents which enable them to be used for the subsequent synthesis of complex alkaloid molecules (of magnoline, dauricine, etc, types).

Diphenyl ethers (I-IV) containing a methoxymethyl group in the meta position in one of the benzene rings were synthesized. Such compounds were then converted, through the corresponding bromide (V) into phenoxy derivatives of benzyl cyanide (VI), which on saponification form dicarboxylic acids [4] (VII):



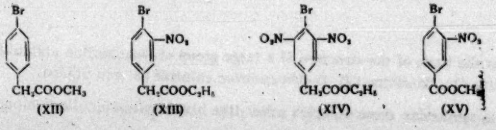


The phenolic component for the synthesis was the methyl ether of m-hydroxybenzyl alcohol, which was prepared according to the following scheme:



(VIII) (IX) (X) (XI)

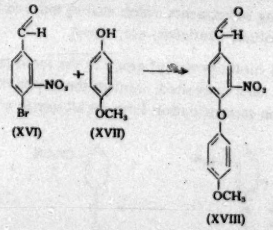
The other components in the synthesis were esters of 4-bromo-, 3-nitro-4-bromo-, and 3,5-dinitro-4-bromophenylacetic acids (XII, XIII, XIV) and of 3-nitro-4-bromobenzoic acid (XV):



(XII) (XIII) (XIV) (XV)

The diphenyl ethers were synthesized by the reaction between the potassium phenate salt of m-hydroxybenzyl alcohol methyl ether and an aromatic halogenated compound in the presence of a catalyst (copper, or without a catalyst on heating, in some cases in the presence of a solvent.

The reaction conditions were determined by the structure of the halogenated component. The best yields in the mildest conditions were obtained in the reactions with esters of 3,5-dinitro-4-bromophenylacetic acid and 3-nitro-4-bromobenzoic acid. Equally easy was the formation in an aqueous medium, without the use of a catalyst, of the diphenyl ether (XVIII) from 3-nitro-4-bromobenzaldehyde (XVI) and hydroquinone methyl ether (XVII):



(XVI) (XVII) (XVIII)

In the absence of groups which increased the halogen mobility the reaction proceeded at higher temperatures (140-150°) in the presence of a catalyst. In such conditions the yield of 3-methoxymethyl-4-carbomethoxymethyl diphenyl ether reached 35%.

EXPERIMENTAL

m-Nitrobenzyl methyl ether (IX). 60 ml of dimethyl sulfate and 60 ml of 10 N caustic soda solution was added gradually (during 1 hour) to 50 g of m-nitrobenzyl alcohol (VIII) [5] (b.p. 152-155° at 2 mm) and the mixture was heated to 40° with continuous stirring. The stirring was continued 1.5-2 hours at the same temperature, after which the oil layer was separated off and the aqueous layer was extracted with benzene.

The yield of the ether (IX) with b.p. 128-130° (5 mm) was 43.5 g (80%).

Found %: N 8.34, 8.73. $C_8H_9O_3N$. Calculated %: N 8.38.

After vacuum distillation of the crude ether (IX) some dark colored oil which congealed on standing usually remained in the flask. After 2-fold recrystallization from alcohol a colorless substance with m.p. 100-102° was isolated, the analytical data for which corresponded to 4,4'-dinitro dibenzyl ether.

Found %: N 9.80. $C_{14}H_{13}O_5N_3$. Calculated %: N 9.78.

Methyl m-aminobenzyl ether (X). 41.75 g of methyl m-nitrobenzyl ether (IX) was dissolved in 180 ml of methyl alcohol, 250 ml of concentrated hydrochloric acid was added, followed by about 125 g of zinc dust (at 25-30°) gradually with stirring. The excess zinc dust was filtered off; the filtrate was diluted with water, neutralized by concentrated caustic soda solution, and extracted with ether. The yield of ether (X) was 27.4 g (80%).

B.p. 115-118° (1-2 mm); d_4^{20} 1.067, n_D^{20} 1.5635, MR_D 41.73; calculated: 41.50.
Found %: N 10.26, 10.48. $C_8H_{11}ON$. Calculated %: N 10.21.

The ether may also be prepared by catalytic hydrogenation of the ether (IX) over Raney nickel catalyst under 65 atmospheres pressure at 20-25°. The yield is 86.5%.

Methyl m-hydroxybenzyl ether (XI). 15 g of methyl m-aminobenzyl ether (X) was dissolved in 100 ml of 30% sulfuric acid and 35 ml of 20% sodium nitrite solution was gradually added at a temperature between −5 and +3°. At the end of the diazotization a small amount of urea was added and the solution was added dropwise with stirring to 200 ml of 30% sulfuric acid solution heated on a boiling water bath. The solution was cooled and the reaction product was extracted with ether. The yield of the ether (XI) was 9.1 g (60%).

B.p. 119-120° (4 mm), d_4^{20} 1.108, n_D^{20} 1.5400, MR_D 39.08; calculated: 38.71.
Found %: C 69.44, 69.64; H 7.51, 7.54. $C_8H_{10}O_2$. Calculated %: C 69.56; H 7.25.

3,5-Dinitro-4-bromophenylacetic acid. 13 g of 3-nitro-4-bromophenylacetic acid [6] (m.p. 112-113°) was added gradually to 130 ml of nitric acid (d 1.503). The solution was heated 1 hour on the boiling water bath and after cooling poured onto ice. 3,5-Dinitro-4-bromophenylacetic acid forms pale yellow crystals (from alcohol), m.p. 162-163°. Yield 10 g (65%).

3,5-Dinitro-4-bromophenylacetic acid was also prepared by the nitration of 4-bromophenylacetic acid [7] (m.p. 111-112°) in the same conditions, with 50% yield calculated on the 4-bromophenylacetic acid.

Found %: N 9.12, 9.34. $C_8H_5O_6N_2Br$. Calculated %: N 9.18.

Ethyl ester of 3-nitro-4-bromophenylacetic acid (XIII). 10 g of 3-nitro-4-bromophenylacetic acid [7] was dissolved in 30 ml of anhydrous alcohol, 50 ml of anhydrous benzene and 1 ml of sulfuric acid (d 1.84) was added, and the mixture heated on the boiling water bath 5 hours with continuous distillation of the benzene to remove water. The benzene and excess alcohol were partly removed under vacuum, and the residue was diluted with 3 times its own amount of water and ice and extracted with ether. The yield of the ester (XIII), b.p. 156-159° (1-2 mm) was 8.3 g (75%). Upon prolonged storage lasting several months the liquid congealed into crystals, m.p. 33-35°.

Found %: N 5.16, 4.79. $C_{10}H_{10}O_{11}NBr$. Calculated %: N 4.86.

Ethyl ester of 3,5-dinitro-4-bromophenylacetic acid (XIV). A solution of 5 g of 3,5-dinitro-4-bromophenylacetic acid in 20 ml of anhydrous alcohol was boiled 3 hours while a stream of hydrogen chloride was passed through continuously. After cooling the reaction mass was poured into water. The precipitated crystals were filtered off and recrystallized from alcohol. M.p. 75-76°. The yield was almost quantitative.

Found %: N 8.28, 8.27. $C_{10}H_9O_6N_2Br$. Calculated %: N 8.40

3-Nitro 4-(4'-methoxyphenoxy)benzaldehyde (XVIII)*. 0.28 g of caustic potash was dissolved in 1.8 ml of water, 1.15 g of 3-nitro-4-bromobenzaldehyde [8] (XVI) (m.p. 102-103°) and 0.62 g of hydroquinone monomethyl ether (XVII) was added, and the reaction mass was heated 3 hours at 118-120°. The disubstituted diphenyl ether formed was extracted with chloroform and the extract was washed with 3% caustic soda solution. After removal of the chloroform the residue was recrystallized from anhydrous alcohol. M.p. 62-63°. Yield 0.7 g (53%).

Found %: N 5.17, 5.13. $C_{14}H_{11}O_5N$. Calculated %: N 5.13.

3-Nitro-4-bromobenzaldehyde semicarbazone was obtained from 7 times its own volume of methanol, m.p. 221-222°.

Found %: N 19.25. $C_8H_7O_3N_4Br$. Calculated %: N 19.51.

3-Nitro-4-(4'-methoxyphenoxy)benzaldehyde semicarbazone was obtained from 10 times its own volume of methanol, m.p. 201-202°.

Found %: N 16.80, 17.20. $C_{15}H_{14}O_5N_4$. Calculated %: N 16.97.

* Experiment carried out jointly with V. Kolyakova.

3-Methoxymethyl 2'-nitro-4'-carbomethoxy diphenyl ether (IV).* 2.65 g of methyl m-hydroxybenzyl ether (XI) was dissolved in 30 ml of anhydrous benzene and 0.45 g of sodium was added. When the sodium dissolved, part of the benzene (10-15 ml) was distilled off under vacuum, 5 g of the methyl ester of 3-nitro-4-bromobenzoic acid (XV) (m.p. 102-103°) was added, and the mixture was heated 12 hours on the boiling water bath. The benzene solution was washed with 3% caustic soda solution. The residue after removal of benzene was purified chromatographically (on aluminum oxide). Yield 4.65 g (77.3%). The product is a yellow oil which does not set on cooling and which does not distil at 1-2 mm.

Found %: N 4.37. $C_{16}H_{15}O_6$. Calculated %: N 4.41.

3-Methoxymethyl 4'-carbomethoxymethyl diphenyl ether (I). 21 g of methyl m-hydroxybenzyl ether (XI) was added to a solution of 8.5 g of caustic potash in 25 ml of anhydrous methanol. The methanol was distilled off under vacuum. For complete removal of moisture from the phenate, 2-3 lots of 10 ml of benzene were added and subsequently distilled off and the mixture was then held in vacuum 2 hours at 150°. 1 g of freshly prepared catalyst (copper powder) [9] and 69 g of the methyl ester of 4-bromophenylacetic acid (XII) (b.p. 129-131°, 7 mm) was added to the dry residue. The mixture was heated in a stream of nitrogen at 140-145° for 3.5 hours. It was diluted with 2% caustic soda solution and extracted with ether. Yield 15.19 g (35%).

B.p. 180-182° (1-2 mm); d_4^{20} 1.1471, n_D^{20} 1.5539, MR_D 79.98; calculated 78.44 ••.
Found %: C 70.92, 71.06; H 6.18, 6.15. $C_{17}H_{18}O_4$. Calculated %: C 71.32; H 6.29.

3-Methoxymethyl 4'-carboethoxymethyl diphenyl ether is a colorless thick liquid.

B.p. 184-186° (1-2 mm), d_4^{20} 1.1307, n_D^{20} 1.5465, MR_D 84.02; calculated: 83.06 ••.

3-Methoxymethyl 2'-nitro-4'-carboethoxymethyl diphenyl ether (II). The starting materials for the synthesis were the ethyl ester of 3-nitro-4-bromophenylacetic acid (XIII) and methyl m-hydroxybenzyl ether (XI). The reaction was carried out in a manner quite analogous to that for the ether (I). Yield 92%.

The ether (II) is a yellow viscous liquid which decomposes during vacuum distillation (1-2 mm). It was purified chromatographically on aluminum oxide. On prolonged storage it sets into a solid, easily fusible mass.

Found %: N 4.33, 4.23. $C_{18}H_{19}O_6N$. Calculated %: N 4.06.

3-Methoxymethyl 2',6'-dinitro-4'-carboethoxymethyl diphenyl ether (III). 1.38 g of methyl hydroxybenzyl ether (XI) was dissolved in 15 ml of anhydrous benzene and 0.23 g of sodium was added. After the sodium dissolved completely, 3.33 g of the ethyl ester of 3,5-dinitro-4-bromophenylacetic acid (XIV) was added with warming. The reaction proceeded 6 hours at the boiling point of benzene. The reaction mass was cooled, diluted with water, the benzene layer was separated off and washed with 2% caustic soda solution.

The ether (III) forms yellowish crystals, with m.p. 97-98° after recrystallization from alcohol. Yield 3.52 g (90%).

Found %: N 7.30, 7.11. $C_{18}H_{18}O_8N_2$. Calculated %: N 7.18.

SUMMARY

1. Certain disubstituted diphenyl ethers, used as intermediates for the synthesis of bisbenzyltetrahydroisoquinoline alkaloids, were prepared and described.

2. Several intermediates for the synthesis of substituted diphenyl ethers were prepared and described.

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• Experiment carried out jointly with L. Chuvilina.

•• A deviation of the molecular refraction found from the calculated value is also observed in the case of unsubstituted diphenyl ether [10]: d_4^{20} 1.074, n_D^{20} 1.5809, MR_D 52.90; calculated: 52.06

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SYNTHESES AND TRANSFORMATIONS OF PYRIMIDINE DERIVATIVES

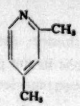
VI. MUTUAL INFLUENCE OF OH AND CH_3 GROUPS IN THE α- OR γ- POSITIONS IN THE PYRIDINE OR PYRIMIDINE NUCLEUS

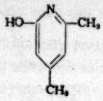
N. V. Khromov-Borisov, R. S. Karlinskaya, and L. N. Ageeva

The hydrogen atoms in methyl groups in the α- or γ- positions in the pyridine or pyrimidine nucleus have increased mobility [1].

In the present paper we examine the extent to which the hydrogen atom mobility in such activated methyl groups is changed when hydroxyl groups are introduced in the meta position relative to them.

Pyridine derivatives. The activities of the methyl groups in 2,4-dimethylpyridine (I), 2,4-dimethyl-6-hydroxypyridine (II), and 2,4-dimethyl-5-nitro-6-hydroxypyridine (III) were compared.


(I)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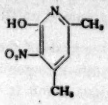
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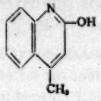
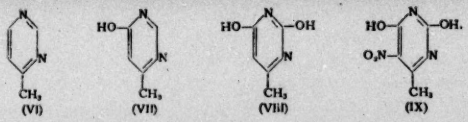

(V)

2,4-Dimethylpyridine (I) can condense with aldehydes to form mono- and distyryl derivatives of pyridine [2]. Attempts to bring about such condensation of 2,4-dimethyl-6-hydroxypyridine (II) with aldehydes were not successful. The reaction did not occur even with p-dimethylaminobenzaldehyde, which has high reactivity in such condensations, despite the use of very harsh conditions (see Experimental Section). Evidently the hydroxyl group in this compound lowers the activity of the methyl groups in the meta position relative to it. In 2,4-dimethyl-5-nitro-6-hydroxypyridine (III) the deactivating influence of the hydroxyl is nullified by the activating influence of the nitro group; this compound can be condensed with either one or two molecules of p-dimethylaminobenzaldehyde according to the reaction conditions. The properties of the condensation products obtained are described in the Experimental Section.

Quinoline derivatives. In this series, the activities of methyl groups in 4-methylquinoline (IV) and 2-hydroxy-4-methylquinoline (V) were compared.

4-Methylquinoline (IV) is capable of condensing with aldehydes by virtue of its active methyl group [3]. We attempted to condense 2-hydroxy-4-methylquinoline (V) with benzaldehyde and with p-dimethylaminobenzaldehyde; however, successful results were not obtained either by fusing the reagents together or by prolonged boiling in aniline solution. Here also the methyl group lost its activity under the influence of the hydroxyl group.

Pyrimidine derivatives. In the pyrimidine series we studied the activity of the methyl group in 4-methylpyrimidine (VI), 6-hydroxy-4-methylpyrimidine (VII), 2,6-dihydroxy-4-methylpyrimidine (VIII), and 2-6-dihydroxy-4-methyl-5-nitropyrimidine (IX):



(VI) (VII) (VIII) (IX)

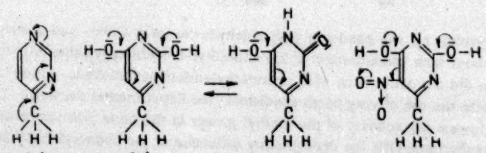
All these compounds can condense with aldehydes, but with different degrees of ease. For example, 4--methylpyrimidine (VI) condenses even with benzaldehyde; when the substances are heated together in the presence of a small amount of zinc chloride, 4-styrylpyrimidine is formed [4]. Mono- and dihydroxypyrimidine, (VII) and (VIII), cannot be condensed with benzaldehyde even in the most harsh conditions. They condense with p-dimethylaminobenzaldehyde in boiling aniline [5]; with 6-hydroxy-4-methylpyrimidine (VII) the reaction takes 6 hours, and with 2,6-dihydroxy-4-methylpyrimidine (VIII), 24 hours. 2,6-Dihydroxy-4-methyl-5-nitropyrimidine (IX) condenses with p-dimethylaminobenzaldehyde simply upon fusion of the reagents [6].

The behavior of these substances (VI, VII, VIII, IX) with p-nitrodiazobenzene is also significant. 4-Methylpyrimidine (VI) in glacial acetic acid solution in presence of anhydrous sodium acetate undergoes an azo coupling reaction with p-dinitrodiazobenzene, forming 4-(p-nitrobenzeneazomethyl)pyrimidine. 6-Hydroxy-4-methylpyrimidine (VII) does not enter such a reaction either in glacial acetic acid in presence of sodium acetate, or in pyridine. 2,6-Dihydroxy-4-methylpyrimidine (VIII) reacts with p-nitrodiazobenzene to form 2,6-dihydroxy-4--methyl-5-p-nitrobenzeneazopyrimidine [6]. The methyl group remains unaffected. Therefore the activity of the methyl group decreases with the appearance of hydroxyl groups in the 2 and 6 positions.

In 2,6-dihydroxy-4-methyl-5-nitropyrimidine (IX) the methyl group regains its lost activity; with p--nitrodiazobenzene it forms 2,6-dihydroxy-5-nitro-4-(p-nitrobenzeneazomethyl)pyrimidine [6].

Thus here, as in the pyridine series, the activity of the methyl group is decreased if hydroxyl groups are introduced into the meta position relative to it. If a nitro group is also introduced in the ortho position relative to the methyl, the deactivating effect of the hydroxyl groups is nullified in this case also.

These effects can be explained as follows on the basis of the electron displacement theory: the positive charges which arise under the influence of the heterocyclic nitrogen atoms at the even positions in the pyrimidine (or pyridine) ring cause increased mobility of the hydrogen atoms in the methyl group (σ, π-conjugation) (X):



(X) (XI) (XII) (XIII)

In dihydroxymethylpyrimidine (XI) these charges are partly compensated by the displacement of the unshared electro pairs of the oxygen atoms (hydroxyl conjugation effect). This displacement is sometimes so great that a double bond is formed between O and C (XII) [7]. Under the influence of the nitro group (XIII) the positive charges at the even positions increase, and in this manner the nitro group opposes the deactivating influence of the hydroxyls.

EXPERIMENTAL

Attempts to condense 2,4-dimethyl-6-hydroxypyridine with p-dimethylaminobenzaldehyde. In each experiment 1.23 g of 2,4-dimethyl-6-hydroxypyridine (0.01 mole) and 2.72 g of p-dimethylaminobenzaldehyde (0.02 mole) was taken. The experiments were carried out in the following conditions:

1) the reagents were boiled 3 hours in 25 ml of ethyl alcohol with the addition of 3 drops of piperidine. When the solution was cooled, the original dimethylhydroxypyridine (m.p. 181°) was precipitated almost quantitatively, and evaporation of the alcohol filtrate yielded 2.3 g of p-dimethylaminobenzaldehyde (m.p. 73°); 2) the same, in 25 ml of isoamyl alcohol; 3) the reagents were fused 3 hours at 200° in the presence of anhydrous sodium

acetate (0.1 g); 4) the same, in presence of anhydrous zinc chloride; 5) the reagents were fused 2 hours at 160° in the presence of piperidine (12 drops); 6) the reagents were boiled in 30 ml of pyridine for 6 hours; 7) the reagents were boiled 6 hours in 30 ml of aniline; 8) the reagents were boiled 6 hours in 30 ml of 7% aqueous alkali (NaOH).

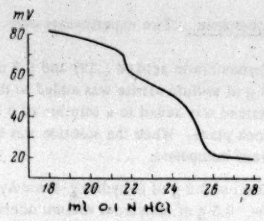
No reaction took place between 2,4-dimethyl-6-hydroxypyridine and p-dimethylaminobenzaldehyde in any of these experiments.

Condensation of 2,4-dimethyl-5-nitro-6-hydroxypyridine with p-dimethylaminobenzaldehyde. The experiments were carried out in the conditions described above.

a) When the reagents were boiled 6 hours in 30 ml of 7% caustic soda under reflux, the solution acquired a bright orange color. The precipitate which formed on cooling was filtered off, dried, and treated with hot alcohol, to remove unreacted aldehyde. The remaining orange crystals were dissolved in a large volume of water and then precipitated by the cautious addition of decinormal hydrochloric acid solution. The orange precipitate so formed was purified by recrystallization from chlorobenzene. The melting point of the purified substance was 267°, yield 1.7 g (57%).

The substance is soluble in hot chlorobenzene and dichloroethane, easily soluble in mineral acids and glacial acetic acid, and insoluble in ether, alcohol, carbon tetrachloride, chloroform, benzene, toluene, acetone, and ligroine.

Found %: C 64.5; H 5.6; N 14.10. $C_{16}H_{17}O_3N_3$. Calculated %: C 64.4; H 5.7; N 14.05.



The substance is acid in character, is soluble in dilute caustic soda, and may be titrated by acids. The acid equivalent of the compound was determined by potentiometric titration with the aid of a glass electrode (see figure).

Found: equiv. 302. $C_{16}H_{17}O_3N_3$. Calculated: M 299.

According to the elementary analysis data and the value found for the molecular weight, the substance is the condensation product of 1 molecule of 2,4-dimethyl-5-nitro-6-hydroxypyridine with 1 molecule of p-dimethylaminobenzaldehyde, and it is therefore 6-hydroxy-2-(or 4-)-methyl-4-(or 2-)-p-dimethylaminostyryl-5-nitropyridine.

b) 1.68 g of 2,4-dimethyl-5-nitro-6-hydroxypyridine (0.01 mole) and 2.72 g of p-dimethylaminobenzaldehyde (0.02 mole) were heated in a beaker in the presence of 12 drops of piperidine. At 160° the reaction mixture melted, and 20 minutes later it set to a dark red mass with a greenish tinge. Recrystallization from benzene yielded a red crystalline substance with m.p. 356-358°. Yield 3.0 g (72%). The substance is soluble in hot benzene, hot dichloroethane, and hot nitrobenzene with a deep red color; it is easily soluble in concentrated mineral acids and glacial acetic acid with a pale yellow color, but is reprecipitated on dilution with water; it is insoluble in carbon tetrachloride, chloroform, benzene, ether, alcohol, toluene, acetone, ligroine, and petroleum ether.

Found %: C 72.5; H 6.3; N 13.4. M 420. $C_{25}H_{26}O_2N_4$. Calculated %: C 72.4; H 6.4; N 13.55. M 414.

By the elementary analysis data and the value found for the molecular weight the substance is the condensation product of 1 mole of 2,4-dimethyl-5-nitro-6-hydroxypyridine with 2 moles of p-dimethylaminobenzaldehyde, and it is therefore 2,4-bis(p-dimethylaminostyryl)-5-nitro-6-hydroxypyridine.

If a carboethoxyl group is placed in position 5 instead of the nitro group, such reactions cannot be carried out; carboethoxyl is evidently too weak in its activating effect in comparison with the nitro group.

Attempts to condense 2-hydroxy-4-methylquinoline with aldehyde were not successful.

a) 1.1 g of hydroxylepidine (2-hydroxy-4-methylquinoline) and 1.4 g of benzaldehyde were heated together 5 hours at 160-180°. Benzaldehyde and benzoic acid were found in the ether extract. The residue insoluble in ether was impure hydroxylepidine, which, after recrystallization from water, was identified by a mixed m.p. determination (m.p. 221-222°).

b) 0.5 g of hydroxylepidine and 0.5 g of p-dimethylaminobenzaldehyde were heated 2 hours at 180-200°. After the melt cooled, p-dimethylaminobenzaldehyde was extracted with alcohol, and hydroxylepidine was extracted from the residue by water.

c) 1.5 g of hydroxylepidine, 2.0 g of p-dimethylaminobenzaldehyde, and 20 ml of aniline were boiled under reflux 22 hours. The precipitate which formed on cooling was filtered after 2 days and washed with alcohol. It was found to be unchanged hydroxylepidine (1.2 g).

Coupling of 4-methylpyrimidine with p-nitrodiazobenzene. 1.1 g of p-nitroaniline was dissolved on heating in 2.4 ml of concentrated hydrochloric acid and 1.4 ml of water. The solution was rapidly cooled and 0.55 g of sodium nitrite dissolved in 3.4 ml of water was added. The resultant diazo solution was added to a solution of 0.8 g of 4-methylpyrimidine in 15 ml of glacial acetic acid. 2.4 g of anhydrous sodium acetate was added with stirring to the colorless solution. The solution became orange in color and a precipitate soon began to form. Gradually the color became deeper and the solution thickened appreciably. The following day the brick-red precipitate was filtered off and washed with water followed by alcohol. Yield 1.0 g (48%).

The azo compound formed was treated several times with boiling water, boiled with 75% acetic acid, and recrystallized from a mixture of acetic anhydride (4 parts) and glacial acetic acid (1 part). The substance has m.p. 208-209°; it is soluble in pyridine and slightly soluble in alcohol, acetic acid, and acetic anhydride. All these solutions have an intensely red color. The substance is insoluble in dioxane, benzene, toluene, chlorobenzene, petroleum ether, ethyl acetate, and acetone. It is slightly soluble in alkalies, forming red-violet or blue-violet solutions, according to the concentration of the alkali. The solutions become decolorized on neutralization.

Found %: N 28.2. $C_{11}H_9O_2N_5$. Calculated %: N 28.7.

Attempts to couple 6-hydroxy-4-methylpyrimidine with p-nitrodiazobenzene. Two experiments were carried out.

a) 0.25 g of p-nitroaniline was dissolved with warming in 0.4 ml of hydrochloric acid (d 1.19) and 0.2 ml of water. The solution was rapidly cooled and a concentrated solution of 0.13 g of sodium nitrite was added to the suspension which formed, with cooling and shaking. The diazo solution so obtained was added to a solution of 0.2 g of 6-hydroxy-4-methylpyrimidine in 5 ml of pyridine; no change of color took place. When the solution was left to stand twenty-four hours, frothing occurred owing to decomposition of the diazo compound.

b) A diazo solution prepared as described above was added to a solution of 0.2 g of 6-hydroxy-4-methylpyrimidine in 6 ml of glacial acetic acid. The solution remained pale yellow. 0.5 g of anhydrous sodium acetate was then added to the solution. No change in color took place during twenty-four hours. When the solution was heated the unreacted diazo compound decomposed.

SUMMARY

1. The effect of hydroxyl groups on the activity of methyl groups in the meta position to each other was studied with the use of 2,4-dimethylpyridine, 4-methylquinoline, 4-methylpyrimidine, and their hydroxy derivatives as examples.

2. It was found that in all the examples studied the hydroxyl groups clearly decrease the mobility of the hydrogen atoms in the methyl groups.

3. The deactivating influence of the hydroxyl groups on the methyl groups is removed by the introduction of a nitro goup in the ortho or para position relative to these groups.

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SYNTHESES WITH THE AID OF ACRYLONITRILE

XXIII. PREPARATION OF N-(γ-ALKOXYPROPYL)PYRROLIDINES AND PIPERIDINES

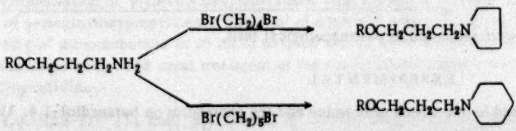
V. G. Yashunsky and A. P. Terentyev

Earlier a simple method was described for the preparation of γ-alkoxypropylamines by the reduction of acrylonitrile by means of metallic sodium in various alcohols [1]. In the present investigation we used these bases for the synthesis of certain substances which might be of interest from the point of view of their physiological activity.

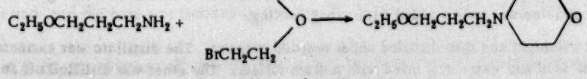
It is known that N- and O-substituted propanolamines are physiologically active substances. For example, homocholine, $(CH_3)_3N-CH_2CH_2CH_2OH$ (OH) has 5 times the activity of choline [2]. According to the literature [3], certain N-piperidyl- and N-pyrrolidylpropanolamines (for example,) have antispasmodic and local anesthetic effects.

Several years ago N,N'-1,3-dipiperidylpropane was prepared by the reaction between 1-(1'-piperidyl)--3-aminopropane and 1,5-dibromopentane [4]. This compound, which showed interesting pharmacological properties, was at the same time highly toxic.

We used an analogous method for the preparation of several tertiary γ-alkoxypropylamines by the condensation of 1,4-dibromobutane with γ-ethoxy, γ-isopropyloxy, γ-isobutoxy, γ-n-butoxy, and γ-isoamyloxypropylamines; and of 1,5-dibromopentane with γ-ethoxy and γ-n-butoxypropylamine. As a result, two series of tertiary bases containing piperidine and pyrrolidine rings were prepared:



In addition it was found that amino ethers with a morpholine ring may be synthesised by an analogous method. γ-Ethoxypropylamine yielded N-(γ-ethoxypropyl)morpholine by the reaction with ββ'-dibromo diethyl ether:



All these amines were prepared for the first time.

Instead of taking 3 moles of amine to one mole of dibromide, as in the classical method [5], we carried out the reaction with equimolecular amounts of the reagents, using potash as the condensing agent. The reaction was carried out in benzene, with boiling lasting many hours. Owing to the use of steam distillation during the treatment, the amines obtained did not contain halogen (Beilstein test). Increased yields of the final products were not obtained when the reaction was carried out in dioxane. It was noted that in the same conditions N-substituted piperidines are obtained in higher yields than their five-membered analogs.

TABLE

Preparation of N-(γ-alkoxypropyl) Cyclic Amines

Amine	Reaction time (hours)	Yield (%)
$C_2H_5O(CH_2)_3N$	17	44.4
iso-$C_3H_7O(CH_2)_3N$	24	46.2
n-$C_4H_9O(CH_2)_3N$	17	36.6 *
	7	31.0
iso-$C_4H_9O(CH_2)_3N$	24	45.5
iso-$C_5H_{11}O(CH_2)_3N$	24	28.7
$C_2H_5O(CH_2)_3N$	20	59.0
n-$C_4H_9O(CH_2)_3N$	27	53.4
$C_2H_5O(CH_2)_5N$O	24	44.8

* γ-Butoxypropylamine and 1,4-dibromobutane were taken in the molar ratio 3:1; the yield is calculated on the dibromide.

The tertiary amines obtained are mobile colorless liquids with a characteristic piperidine odor, are easily soluble in alcohol, benzene and ether, and avidly absorb moisture and carbon dioxide from the air. The hydrochlorides, picrates, methiodides, and chloroplatinates of these compounds are noncrystallizing oils. In the case of N-(γ-butoxypropyl)piperidine the chloroaurate was obtained in the form of bright yellow crystals, m.p. 50.5°. When N-(γ-ethoxypropyl)-pyrrolidine was heated with benzoyl chloride in benzene solution, crystals were obtained which immediately deliquesced in air. With germanotungstic acid, $H_4[Ge(W_2O_7)_6]$, in an acid medium yellow-green precipitates insoluble in water are formed.

Some of the amines obtained were subjected to pharmacological tests.

EXPERIMENTAL

1,4-Dibromobutane was prepared by the action of bromine and red phosphorus on butanediol-1,4. Yield 67.2%, b.p. 75-76° (11 mm).

1,5-Dibromopentane was prepared by the decomposition of N-benzoylpiperidine by means of phosphorus pentabromide [6]. B.p. 98-101° (12 mm).

β,β'-Dibromo diethyl ether [7]. 68.5 g of phosphorus tribromide was placed in a flask fitted with a mechanical stirrer, dropping funnel, and reflux condenser with a calcium chloride tube. A solution of 34.0 g of diethylene glycol in 9.25 g of anhydrous pyridine was slowly added with strong cooling.

The mixture was left overnight and then distilled under reduced pressure. The distillate was extracted with ether, washed with hydrochloric acid and water, and dried with sodium sulfate. The ether was distilled off and the residue was distilled under vacuum. The yield was 53.7 g (72.3 %) of β,β'-dibromo diethyl ether, b.p. 114-115° (33 mm). Literature data: b.p. 115° at 32 mm.

N-(γ-Ethoxypropyl)pyrrolidine. 13.24 g of potash moistened with a few drops of water was placed in a three-necked flask of 50 ml capacity, fitted with a dropping funnel, mechanical stirrer, and reflux condenser, and a solution of 10.36 g of 1,4-dibromobutane in 15 ml of benzene was added. A solution of 4.95 g of γ-ethoxypropylamine in 10 ml of benzene was added dropwise with stirring during an hour to the liquid heated on the water bath. The mixture was then heated 16 hours on the water bath. The liquid in the flask was then acidified and distilled in steam. The acid hydrochloride solution was evaporated to dryness on the water bath and decomposed by solid alkali; the liberated base was extracted with ether and dried with fused caustic potash. The ether was driven off, and the

amine was fractionated under reduced pressure *.

The yield was 3.37 g (44%) of N-(γ-ethoxypropyl)pyrrolidine:

B.p. 64-65° (5 mm), 74-75° (10 mm), n_D^{20} 1.4440, d_4^{20} 0.8856, MR_D 47.17. $C_9H_{19}ON$. Calculated: 47.15.
Found %: C 68.60, 68.68; H 12.12, 12.13. $C_9H_{19}ON$. Calculated %: C 68.74; H 12.18.

N-(γ-Isopropyloxypropyl)pyrrolidine was prepared analogously by heating 4.9 g of γ-isopropyloxypropylamine with 9.1 g of dibromobutane 24 hours in the presence of potash. The yield was 3.28 g (46.2 %) of N-(γ-isopropyloxypropyl)pyrrolidine:

B.p. 79-80° (10 mm), n_D^{20} 1.4476, d_4^{20} 0.8863, MR_D 51.68. $C_{10}H_{21}ON$. Calculated: 51.76.
Found %: C 69.82, 69.98; H 12.41, 12.55. $C_{10}H_{21}ON$. Calculated %: C 70.12; H 12.36.

N-(γ-Isobutoxypropyl)pyrrolidine with b.p. 92.5° (9 mm) was obtained by a similar method in 45.5 % yield:

n_D^{20} 1.4445, d_4^{20} 0.8749, MR_D 56.31. $C_{11}H_{23}ON$. Calculated: 56.38.
Found %: C 70.84, 70.73; H 12.47, 12.45. $C_{11}H_{23}ON$. Calculated %: C 71.30; H 12.51.

N-(γ-Butoxypropyl)pyrrolidine. a) A mixture of 6.75 g of γ-butoxypropylamine, 3.45 g of dibromobutane, and 30 ml of benzene, was heated 17 hours on the boiling water bath. The reaction products were treated as described above. After removal of the ether, the mixture of bases was fractionally distilled under vacuum. Three fractions were collected during a second distillation at 13 mm:

1st, 62-64°, 2.3 g; 2nd, 65-104°, about 0.6 g; 3rd, 104-106°, 1.1 g.

The 1st fraction was unreacted γ-butoxypropylamine, and the 3rd, N-(γ-butoxypropyl)pyrrolidine. The yield was 36.6 % calculated on the dibromide.

b) N-(γ-Butoxypropyl)pyrrolidine was obtained in 31 % yield by the reaction of 6.3 g of γ-butoxypropylamine with 10.37 g of 1,4-dibromobutane with the aid of a method analogous to the preparation of N-(γ-ethoxypropyl)pyrrolidine:

B.p. 90-100° (9 mm), n_D^{20} 1.4448, d_4^{20} 0.8729, MR_D 56.48. $C_{11}H_{23}ON$. Calculated: 56.38.
Found %: C 70.94, 71.00; H 12.68, 12.69. $C_{11}H_{23}ON$. Calculated %: C 71.30; H 12.51.

Condensation of γ-isoamyloxypropylamine with 1,4-dibromobutane in the presence of dioxane. A solution of 5.72 g of γ-isoamyloxypropylamine in 20 ml of ether was added during 1.5 hours with stirring to a boiling solution of 8.42 g of dibromobutane in 25 ml of dioxane and 10 ml of anhydrous ether, and the mixture was heated 23 hours on the water bath. The usual treatment of the condensation products yielded 2.23 g (28.7 %) of N-(γ-isoamyloxypropyl)pyrrolidine:

B.p. 113-115° (11 mm), n_D^{20} 1.4462, d_4^{20} 0.8709, MR_D 61.05. $C_{12}H_{25}ON$. Calculated: 61.00.
Found %: C71.96, 72.08; H 12.84, 12.75. $C_{12}H_{25}ON$. Calculated %: C 72.30; H 12.64.

N-(γ-Ethoxypropyl)piperidine was prepared by the method described above for N-(γ-ethoxypropyl)pyrrolidine, by heating a mixture of 4.12 g of γ-ethoxypropylamine, 10.7 g of 1,5-dibromopentane, and 11.0 g of potash 20 hours in benzene. The reaction mass was saturated with concentrated caustic soda solution and distilled in steam. The distillate, acidified with dilute hydrochloric acid, was again distilled in steam. The residue was evaporated in the water bath and the base was isolated in the usual way. The yield was 4.03 g (59 %) of N-(γ-ethoxypropyl)piperidine:

B.p. 82-83° (9 mm), n_D^{20} 1.4490, d_4^{20} 0.8884, MR_D 57.71. $C_{10}H_{21}ON$. Calculated: 51.76.
Found %: C 69.61, 69.58; H 12.72, 12.64. $C_{10}H_{21}ON$. Calculated %: C 70.12; H 12.36.

N-(γ-Butoxypropyl)piperidine was synthesized by an analogous method from 5.24 g of γ-butoxypropylamine and 9.2 g of dibromopentane in 53.4 % yield:

B.p. 120-121.5° (15 mm), n_D^{20} 1.4508, d_4^{20} 0.8796, MR_D 60.99. $C_{12}H_{25}ON$. Calculated: 61.00.
Found %: C 72.16, 72.24; H 12.76, 12.53. $C_{12}H_{25}ON$. Calculated %: C 72.30; H 12.64.

N-(γ-Ethoxypropyl)morpholine. The reaction between 5.7 g of γ-ethoxypropylamine and 13.0 g of β,β'-

* All the vacuum distillations were carried out in a stream of dry nitrogen.

-dibromodiethyl ether in benzene in the presence of moist potash yielded 4.34 g (44.8%) of N-(γ-ethoxypropyl)morpholine:

B.p. 92-94° (15 mm), n_D^{20} 1.4498, d_4^{20} 0.9534, MR_D 48.80. $C_9H_{19}O_2N$. Calculated: 48.78.
Found %: C 62.05, 62.03; H 11.05, 11.05. $C_9H_{19}O_2N$. Calculated %: C 62.39; H 11.05.

SUMMARY

A method is described for the preparation of pyrrolidine and piperidine derivatives of the type:

$ROCH_2CH_2CH_2NC_4H_8$ and $ROCH_2CH_2CH_2NC_5H_{10}$

from alkoxypropylamines and the corresponding dibromides.

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STUDY OF NEW METHODS FOR THE SYNTHESIS OF QUINUCLIDINE-2-CARBOXYLIC ACID

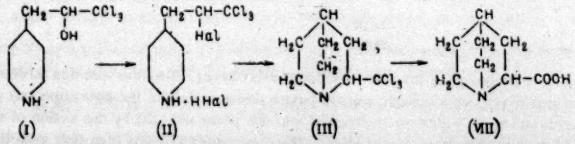
M. V. Rubtsov and E. E. Mikhlina

Quinuclidine-2-carboxylic acid may be used as the starting substance for the preparation of 2-substituted quinuclidines. The literature contains two methods for the synthesis of this acid from tetrahydropyran derivatives [1] and from 4-picoline [2].

In the present study the possibility of preparing quinuclidine-2-carboxylic acid from 4-(β-hydroxy-γ,γ,γ-trichloropropyl)pyridine was investigated. The reduction of the latter in the presence of platinum catalyst (by Adams' method) at room temperature yielded 4-(β-hydroxy-γ,γ,γ-trichloropropyl)piperidine (I). Chlorine atoms were not replaced by hydrogen under those conditions. Partial replacement of chlorine by hydrogen takes place when 4-(β-hydroxy-γ,γ,γ-trichloropropyl)pyridine is treated with zinc dust in dilute acetic acid, with formation of 4-(β-hydroxy-γ,γ-dichloropropyl)pyridine. In the presence of palladium in an acid medium or of Raney nickel catalyst in an alkaline medium, 4-(β-hydroxy-γ,γ,γ-trichloropropyl)pyridine does not react with hydrogen.

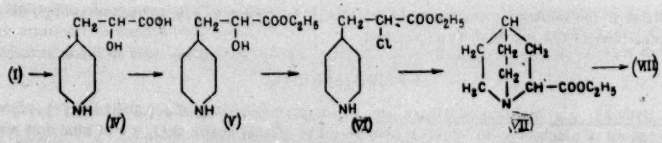
The compound (I) made possible an approach to the synthesis of 2-substituted quinuclidines.

The simplest scheme appeared to be the following:



Experiments showed, however, that the hydroxyl group in (I) is not replaced by halogen either by the action of thionyl chloride under various conditions, or by the action of a mixture of phosphorus pentachloride and phosphorus oxychloride. In the latter case a phosphoric ester is formed. The hydroxyl group could only be replaced by bromine when (I) was heated with 68% hydrobromic acid at 120°. The resultant 4-(β-bromo-γ,γ,γ-trichloropropyl)piperidine (II, Hal = Br) when shaken with an aqueous solution of soda in chloroform was converted into 2-trichloromethylquinuclidine (III) in a low yield.

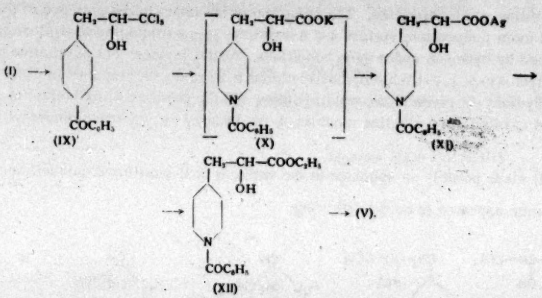
The second scheme proposed for an approach to the synthesis of quinuclidine-2-carboxylic acid was the following:



Saponification of (I) by alcoholic caustic potash solution yielded β-(piperidyl-4)lactic acid (IV). Acrylic acid was not formed even when (IV) was heated with caustic potash at 200°. Esterification of the acid (IV) by means of 4% alcohol solution of hydrogen chloride resulted in the formation of a solid amorphous substance of a polymeric nature. Prolonged heating of the latter with 10% alcohol solution of hydrogen chloride yielded an oil-like compound the analytical data for which corresponded to the ethyl ester of β-(piperidyl-4)lactic acid (V). The liquid ester (V) after standing 3 months was converted into a white crystalline substance the composition of which also agreed with the ethyl ester of β-(piperidyl-4)lactic acid and which had the same melting point as the amorphous polymer. Brief heating of the crystalline substance with 4% alcohol solution of hydrogen chloride again converted it into the liquid ester. Evidently the crystalline compound, like the amorphous substance, is a polymer of the ester (V), but with a lower degree of polymerization, owing to which it is depolymerized much more easily.

The liquid ester (V) was treated with thionyl chloride in order to prepare the ethyl ester of α-chloro-β-(piperidyl-4)propionic acid (VI); hydroxyl groups were substituted by chlorine to an extent of about 20-25%. In view of the difficulty in separating the chlorinated ester (VI) from the original ester (V), a mixture of the two substances was treated with pyridine in order to close the quinuclidine ring. Saponification of the cyclization products resulted in formation of quinuclidine-2-carboxylic acid (VIII), obtained in 12-15% yield calculated on the ester (V) taken; the residue after separation of (VIII) was converted into the original ester (V). This was benzoylated to convert it into the ethyl ester of β-(N-benzoylpiperidyl-4)lactic acid (XII) and reacted with thionyl chloride. However, here again the hydroxyl groups were only partially replaced by chlorine.

The ester (V) was also prepared according to the following scheme:



The compound (I) was converted into the N-benzoyl derivative (IX) by the reaction with benzoyl chloride in pyridine. Treatment of (IX) by alcoholic caustic potash solution yielded the potassium salt of β-(N-benzoylpiperidyl-4)lactic acid (X), which was converted into the silver salt (XI) by the action of silver nitrate, and then into the ester (XII) with the aid of ethyl iodide. The compound (XII) was identical with the substance obtained by benzoylation of the ester (V). The benzoyl group was saponified by prolonged heating of the ester (XII) with 20% alcohol solution of hydrogen chloride, and also by boiling with 17% hydrochloric acid followed by esterification of the carboxyl group; the liquid ester (V) was obtained. The polymeric ester was not formed in this instance.

It follows from the above that alkaline hydrolysis of the compound (I) and of its N-benzoyl derivative (IX) results in the formation of β-(piperidyl-4)lactic acid (IV); in the first case the polymeric acid is formed; in the second, only the monomeric acid is formed which no longer polymerizes during the subsequent transformations which occur during prolonged heating in an acid or neutral medium (saponification of the benzoyl group, esterification).

In addition to the substances mentioned in the text, 4-(β-hydroxy-γ,γ,γ-trichloropropyl)-N-methyl- and -N-benzylpiperidines (XIII and XIV) were prepared.

EXPERIMENTAL

4-(β-Hydroxy-γ,γ-dichloropropyl)pyridine. To a mixture of 10 g of 4-(β-hydroxy-γ,γ,γ-trichloropropyl)pyridine, 40 ml of alcohol, 10 ml of water, and 16 ml of glacial acetic acid, 9 g of zinc dust was added at 60° during 20 minutes, and the reaction mass was then heated at the boil 3 hours. The colored solution was

decanted from the precipitate, treated with saturated sodium carbonate solution to an alkaline reaction, and repeatedly extracted with ether. The ether solution was dried with sodium sulfate, the ether distilled off, and 0.67 g of 4-(β-hydroxy-γ,γ-dichloropropyl)pyridine was obtained from the residue on cooling. M.p. 134-136° after 2-fold recrystallization from 25% alcohol.

Found %: N 6.77, 6.67; Cl 34.24. $C_8H_9ONCl_2$. Calculated %: N 6.79; Cl 34.46.

4-(β-Hydroxy-γ,γ,γ-trichloropropyl)piperidine (I). A suspension of 12 g of 4-(β-hydroxy-γ,γ,γ-trichloropropyl)pyridine in 185 ml of 1% alcohol solution of hydrogen chloride was reduced in the presence of 0.4 g of platinum oxide. The theoretical amount of hydrogen needed for reduction of the pyridine to the piperidine nucleus was absorbed in the course of 16 hours. The platinum black was removed from the alcohol solution by filtration, the solution was evaporated under vacuum to $^1/_3$ of the original volume, and diluted with ether till turbid. The precipitated 4-(β-hydroxy-γ,γ,γ-trichloropropyl)piperidine hydrochloride was separated and dried in the air. Yield 13.4 g (94.8%). M.p. 194-196° (decomp.). The substance forms colorless crystals, easily soluble in water and alcohol, insoluble in ether and acetone.

Found %: C 34.02, 33.94; H 5.55, 5.62; N 4.86; Cl 49.74. $C_8H_{14}ONCl_3 \cdot HCl$. Calculated %: C 33.92; H 5.3; N 4.94; Cl 50.08.

To prepare the base, a solution of 5.15 g of the hydrochloride of 4-(β-hydroxy-γ,γ,γ-trichloropropyl)piperidine in 10 ml of water was treated with 80 ml of 15% sodium carbonate solution. The yield was 4.49 g (92.5%) of the base. 4-(β-Hydroxy-γ,γ,γ-trichloropropyl)piperidine is insoluble in water, chloroform, and ether, and is easily soluble in alcohol. M. p. 159-160° (decomp.) from alcohol.

Found %: C 39.30, 39.10; H 5.84, 5.75. $C_8H_{14}ONCl_3$. Calculated %: C 38.95; H 5.68.

The hydrobromide forms colorless crystals, easily soluble in water and alcohol, with difficulty in ether. M.p. 188-189° (decomp.).

Found %: N 4.28. $C_8H_{14}ONCl_3 \cdot HBr$. Calculated %: N 4.28.

4-(β-Hydroxy-γ,γ,γ-trichloropropyl)-N-methylpiperidine (XIII). 6.4 g of 4-(β-hydroxy-γ,γ,γ-trichloropropyl)piperidine, 1.84 g of methyl iodide, and 64 ml of anhydrous alcohol were heated together 2 hours at 42-43°. At the end of the heating the solution was evaporated under vacuum. The residue was triturated with 30 ml of water, and the water-insoluble 4-(β-hydroxy-γ,γ,γ-trichloropropyl)-N-methylpiperidine was filtered off. Yield 1.75 g (51.6% on the methyl iodide taken for the reaction). M.p. 172.5-173.5° (from alcohol). It is a white crystalline powder, easily soluble in alcohol, insoluble in ether, chloroform, acetone, and water.

The filtrate after removal of the 4-(β-hydroxy-γ,γ,γ-trichloropropyl)-N-methylpiperidine was treated with 30 ml of 50% potash solution. 2.6 g of the starting substance was obtained.

Found %: C 41.40; H 6.16; N 5.41. $C_9H_{16}ONCl_3$ Calculated %: C 41.46; H 16.14; N 5.37.

4-(β-Hydroxy-γ,γ,γ-trichloropropyl)-N-benzylpiperidine (XIV). 6 g of 4-(β-hydroxy-γ,γ,γ-trichloropropyl)piperidine, 1.54 g of benzyl chloride, and 60 ml of anhydrous alcohol were heated 2 hours at the boil. The alcohol was distilled off under vacuum, the residue was triturated with 30 ml of water, and the 4-(β-hydroxy-γ,γ,γ-trichloropropyl)-N-benzylpiperidine was filtered off. The substance was purified by crystallization from 90% alcohol. M.p. 130-131°. Yield 2.95 g (71.8% on the benzyl chloride taken for the reaction). 2.25 g of the original substance was obtained from the filtrate.

Found %: C 53.57, 53.30; H 5.77, 5.66; N 4.17, 4.16. $C_{15}H_{20}ONCl_3$. Calculated %: C 53.40; H 5.94; N 4.16.

Phosphoric ester of 4-(β-hydroxy-γ,γ,γ-trichloropropyl)piperidine. 2 g of 4-(β-hydroxy-γ,γ,γ-trichloropropyl)piperidine, 15 ml of phosphorus oxychloride, and 1.5 g of phosphorus pentachloride were heated together 2 hours at the boil. The phosphorus oxychloride was then distilled off under vacuum, the residue was dissolved in ether, the ether solution was washed with water and with saturated sodium bicarbonate solution, and dried with sodium sulfate. After removal of ether a colorless oil was obtained, easily soluble in organic solvents and insoluble in water.

Found %: P 9.15. $C_8H_{13}PO_3NCl_5$. Calculated %: P 8.55.

4-(β-Bromo-γ,γ,γ-trichloropropyl)piperidine (II). 0.5 g of 4-(β-hydroxy-γ,γ,γ-trichloropropyl)piperidine and 15 ml of 68% hydrobromic acid were heated 3 hours in a sealed tube at 120°. The reaction solution was then evaporated under vacuum till crystallization started, the crystals were separated off and recrystallized from

alcohol. The yield was 0.32 g (40.6 %) of 4-(β-bromo-γ,γ,γ-trichloropropyl)piperidine hydrobromide. It forms white crystals, soluble with difficulty in water and alcohol, insoluble in acetone and ether. M.p. 166-166.5° (decomp.).

Found %: N 3.46. $C_8H_{13}NCl_3Br \cdot HBr$. Calculated %: N 3.58.

2-Trichloromethylquinuclidine (III). 15 ml of 15% sodium carbonate solution and 20 ml of chloroform was added to a suspension of 1 g of 4-(β-bromo-γ,γ,γ-trichloropropyl)piperidine hydrobromide in 12 ml of water. The mixture was shaken 3 hours. The chloroform layer was separated off and the aqueous layer was extracted with chloroform. The combined chloroform solutions were dried with sodium sulfate. After removal of the chloroform 0.3 g of oily crystals remained. These were dissolved in 5 ml of anhydrous alcohol, and the alcohol solution was diluted with 20 ml of anhydrous ether. The dark flocculent precipitate was filtered off, and the filtrate was treated with an alcohol solution of hydrogen chloride till acid to congo. The white, hygroscopic crystals which formed were filtered off and purified by recrystallization from alcohol-ether mixture. M. p. 230° (decomp.).

Found %: N 4.24, 4.08; Cl 44.08, 44.87. $C_8H_{12}NCl_3 \cdot HCl \cdot 3H_2O$. Calculated %: N 4.39; Cl 44.45.

β-[Piperidyl-(4)]lactic acid (IV). 91 g of caustic potash dissolved in 45 ml of anhydrous alcohol was added to a suspension of 5 g of 4-(β-hydroxy-γ,γ,γ-trichloropropyl)piperidine in 50 ml of anhydrous alcohol. The reaction mass was heated 4 hours on the water bath at 40-45°, then cooled, and carbon dioxide was passed through at room temperature till the jellylike mass originally formed was converted into a fine crystalline powder. The inorganic salts were separated and washed with anhydrous alcohol. The alcohol solution was evaporated to dryness under vacuum, and the residue was dissolved in 3 ml of 10% hydrochloric acid. The hydrochloric acid solution was evaporated under vacuum, and the hydrochloride of β-[piperidyl-(4)]lactic acid was extracted from the solid residue by anhydrous alcohol. The alcohol solution was diluted with anhydrous ether. The hygroscopic yellow-grey precipitate which formed was washed several times by decantation with ether, separated, and dried in a vacuum desiccator. Yield 3.3 g (61.8%). M.p. 202-204° (decomp.). It is an amorphous yellow-grey hygroscopic powder, easily soluble in water and alcohol.

Found %: Cl 13.79, 13.61. $C_8H_{15}O_2N \cdot HCl \cdot H_2O$. Calculated %: Cl 13.48.

Ethyl ester of β-[piperidyl-(4)]lactic acid (V). 2.7 g of β-[piperidyl-(4)]lactic acid hydrochloride, dried under vacuum at 120-130°, was heated 3 hours at the boil with 27 ml of 4% alcohol solution of hydrogen chloride. The alcohol solution was evaporated under vacuum, and the residue was treated with 50% potash solution and extracted with chloroform. The chloroform solution was dried with potash, the chloroform was distilled off, and the remaining glassy mass hardened when rubbed with a rod. The yield was 2.5 g of a yellow powder, easily soluble in water, alcohol, and chloroform, insoluble in ether or acetone. After reprecipitation from alcohol by means of ether the substance melts at 230° with decomposition.

The substance was heated 30 hours with 30 ml of a 10% solution of hydrogen chloride in alcohol. The alcohol was distilled off, and the residue was treated with 50% potash solution and extracted with ether. After removal of the ether the residue was distilled under vacuum. B.p. 147-148° (12 mm), n_D^{20} 1.4628. It is a colorless mobile liquid, easily soluble in water and in organic solvents. Yield 0.7 g (27%).

Found %: C 59.91, 60.04; H 9.66, 9.85; N 6.66. $C_{10}H_{19}O_2N$. Calculated %: C 59.71; H 9.46; N 6.90.

The ethyl ester of β-[piperidyl-(4)]lactic acid became converted into a white crystalline mass after standing 3 months. This was triturated with ether and filtered. After two-fold purification from alcohol-ether mixture the substance had m.p. 230-231°. It is a white crystalline powder, easily soluble in water and alcohol, insoluble in ether and in acetone.

Found %: C 59.56; H 9.58. $C_{10}H_{19}O_2N$. Calculated %: C 59.71; H 9.46.

Conversion of the crystalline substance into the liquid ethyl ester of β-[piperidyl-(4)]lactic acid. 1 g of the crystalline substance and 10 ml of 4% hydrogen chloride solution in alcohol was heated 3 hours at the boil. The alcohol was distilled off under vacuum, and the residue was treated with 50% potash solution and extracted with ether. The ether solution was dried with potash, the ether was distilled off, and the residue was distilled under vacuum. B.p. 147-148° (12 mm), n_D^{20} 1.4628.

Ethyl ester of β-[N-benzoylpiperidyl-(4)]lactic acid. (XII). 0.97 g of benzoyl chloride was added at room temp. to a solution of 0.92 g of the liquid ethyl ester of β-[piperidyl-(4)]lactic acid in 9 ml of pyridine. The reaction mass became green in color. The solution was stirred 2 hours, the pyridine was distilled off under vacuum, and the

residue was treated with 8 ml of 10 % hydrochloric acid and extracted with ether. The ether solution was washed with 6% soda solution to remove benzoic acid, and dried with sodium sulfate. After removal of the ether the residue was distilled under vacuum. M.p. 175-177° (0.34 mm), n_D^{19} 1.518. It is a colorless, very viscous liquid, easily soluble in organic solvents, insoluble in water. Yield 1.2 g (85.7%).

Found %: C 66.90; H 7.80. $C_{17}H_{23}O_4N$. Calculated %: C 66.88; H 7.56.

Quinuclidine-2-carboxylic acid (VIII). 4 ml of 20% solution of hydrochloric acid in alcohol was added to a solution of 4.4 g of the ethyl ester of β-[piperidyl-(4)]lactic acid in 20 ml of anhydrous ether. The solution was evaporated under vacuum, the residue was dissolved in 20 ml of dry chloroform, 20 ml of thionyl chloride was added, and the reaction mass was heated 6 hours at 62-63°. The chloroform and the excess thionyl chloride was distilled off under vacuum, and the residue was treated with 50% potash solution and extracted with ether. The ether solution was dried a short time with sodium sulfate, the ether was distilled off, and the residue heated 2 hours at the boil with 8 ml of pyridine. The pyridine was removed, and the residue was treated with 10 ml of 50% potash solution and extracted with ether. The ether solution was dried with potash, the ether was distilled off, and the liquid which remained was distilled under vacuum. B.p. 137-147° (12 mm). Yield 1.85 g.

The ester so formed was boiled 5 hours with 18 ml of 17% hydrochloric acid. The hydrochloric acid solution was evaporated under vacuum. The precipitated crystals of quinuclidine-2-carboxylic acid were removed by suction, washed with acetone, and dried in air. Yield 0.2 g. M.p. 286° (decomp.). Rubtsov [2] reported m.p. 292° (decomp.).

Treatment of the residue after removal of quinuclidine-2-carboxylic acid. The filtrate after removal of the quinuclidine-2-carboxylic acid was evaporated under vacuum, the residue was dried by addition and removal under vacuum of anhydrous benzene, and then esterified by warming it with 5% solution of hydrogen chloride in alcohol. The usual treatment yielded a mobile oily liquid, which was distilled under vacuum. B.p. 147-148° (12 mm), n_D^{20} 1.4628. The physical constants for this liquid agree with those of the ethyl ester of β-[piperidyl-(4)]-lactic acid.

4-(β-Hydroxy-γ,γ,γ-trichloropropyl)-N-benzoylpiperidine (IX). 5.1 g of benzoyl chloride was added in 15 minutes to a solution of 6 g of 4-(β-hydroxy-γ,γ,γ-trichloropropyl)piperidine in 60 ml of dry pyridine at 18-20° with thorough stirring. The colorless solution gradually turned green. After addition of the benzoyl chloride the reaction mass was stirred a further 2 hours. The pyridine was then distilled off under vacuum, the residue triturated thoroughly with 50 ml of 10% hydrochloric acid, the aqueous layer decanted off, and the residue again suspended in 50 ml of 10% hydrochloric acid. The greenish crystals were washed with water and then with ether. Yield 8 g (93.8%). After two recrystallizations from alcohol white crystals with m.p. 177-179° were obtained. The substance is easily soluble in chloroform, with difficulty in alcohol and acetone, and is insoluble in water and ether.

Found %: C 51.68, 51.66; H 5.24, 5.15. $C_{18}H_{18}NO_2Cl_3$. Calculated %: C 51.36; H 5.14.

Silver salt of β-[N-benzoylpiperidyl-(4)]lactic acid (XI). To a solution of 8 g of caustic potash in 75 ml of anhydrous alcohol a solution of 6.25 g of 4-(β-hydroxy-γ,γ,γ-trichloropropyl)-N-benzoylpiperidine in 125 ml of anhydrous alcohol was added. The reaction mass was left 48 hours at room temperature. In this time the solution became bright orange in color. Carbon dioxide was then passed till the jelly-like mass first formed was converted into a crystalline powder. The inorganic salts were separated off and washed on the filter with anhydrous alcohol. The filtrate was evaporated to dryness under vacuum. The residue, which was a frothy brown mass, was the potassium salt of β-[N-benzoylpiperidyl(4)]lactic acid. It was dissolved in 10 ml of water, the aqueous solution was extracted 3 times with small amounts of ether, brought to the boil, and poured into a beaker containing 10 ml of hot water. A hot solution of 3.03 g of silver nitrate in 4 ml of water was added at the same time. The nearly white silver salt was precipitated; this darkened very quickly and became dark grey. The silver salt was separated off, washed with water, and dried in air. Yield 6.4 g (93.5%). The silver salt is insoluble in water, ether, and acetone, and is soluble with difficulty in alcohol.

Ethyl ester of β-[N-benzoylpiperidyl-(4)]lactic acid (XII). 9 g of the silver salt of β-[N-benzoylpiperidyl-(4)]lactic acid, 5.1 g of ethyl iodide, and 70 ml of anhydrous ether was heated 6 hours at the gentle boil. The reaction mixture was stirred at intervals. The ether solution was then filtered to remove silver iodide and the latter was thoroughly washed with ether. The combined ether solutions were evaporated under vacuum. The yield was 6.25 g (87.5%) of the ethyl ester of β-[N-benzoylpiperidyl-(4)]lactic acid. B.p. 175° (0.34 mm), n_D^{19} 1.518. It is a colorless, very viscous liquid, easily soluble in the common organic solvents.

Ethyl ester of β-[piperidyl-(4)]lactic acid (V). a) 3 g of the ethyl ester of β-[N-benzoylpiperidyl-(4)]-

-lactic acid and 30 ml of 17% hydrochloric acid was heated 4 hours at the boil. The cooled solution was extracted with ether to remove benzoic acid. The hydrochloric acid solution was decolorized by means of charcoal and evaporated under vacuum. The residue was dried by 3-fold addition and removal of anhydrous alcohol, and then boiled 3 hours with 25 ml of a 5% solution of hydrogen chloride in alcohol. The alcohol was then driven off under vacuum, 15 ml of 50% potash solution was added to the residue, and the resultant oil was extracted with ether. The ether solution was dried with potash, the ether was removed, and the residue distilled under vacuum. B.p. 147-148° (12 mm), n_D^{20} 1.4628. Yield 1.25 g (63.7%). The ester polymerizes on standing.

b) 3.45 g of the ethyl ester of β-[N-benzoylpiperidyl-(4)]lactic acid and 25 ml of a 20% solution of hydrogen chloride in alcohol was heated 30 hours at the boil. The alcohol was then distilled off under vacuum, the residue treated with 30 ml of water, and extracted with ether to remove benzoic acid and unreacted ethyl ester of β-[N--benzoylpiperidyl-(4)]lactic acid. 0.86 g of the latter was obtained. The hydrochloric acid solution was treated with 50% potash solution and extracted with ether. The ether solution was dried with calcined potash, the ether was removed, and the residue distilled under vacuum. B.p. 147-148° (12 mm). The yield was 1.36 g (77.3%) of the ethyl ester of β-[piperidyl-(4)]lactic acid.

SUMMARY

1. The possibility of synthesizing quinuclidine-2-carboxylic acid from 4-(hydroxy-γ,γ,γ-trichloropropyl)-piperidine was studied. It was found that quinuclidine-2-carboxylic acid is formed in low yield because of the great difficulty with which hydroxyl is replaced by halogen both in 4-(β-hydroxy-γ,γ,γ-trichloropropyl)piperidine and in the ethyl ester of β-[piperidyl-(4)]lactic acid and its N-benzoyl derivative.

2. It was found that alkaline hydrolysis of 4-(β-hydroxy-γ,γ,γ-trichloropropyl)piperidine leads to the formation of polymeric β-[piperidyl-(4)]lactic acid. Esterification of this acid yields the polymeric ethyl ester of β-[piperidyl-(4)]lactic acid. When the latter is heated a long time with an alcohol solution of hydrogen chloride, it is converted into the monomeric ester, which again polymerizes on standing. Alkaline hydrolysis of 4-(β-hydroxy--γ,γ,γ-trichloropropyl)-N-benzoylpiperidine results in the formation only of monomeric β-[piperidyl-(4)]lactic acid.

3. 4-(β-Hydroxy-γ,γ,γ-trichloropropyl)-N-methyl- and -benzylpiperidine and a number of conversion products of 4-(β-hydroxy-γ,γ,γ-trichloropropyl)piperidine were synthesized.

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SYNTHESIS OF β-(QUINUCLIDYL-2)-PROPIONIC ACID

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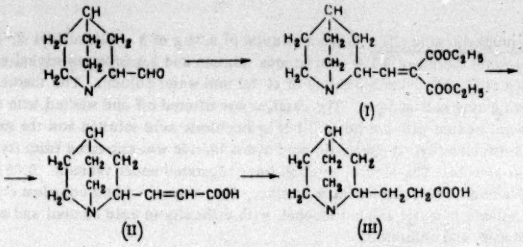
The simple method recently developed by one of the present authors jointly with M. I. Dorokhova [1] for the preparation of quinuclidine-2-carboxylic acid made it possible to study a number of 2-substituted quinuclidines.

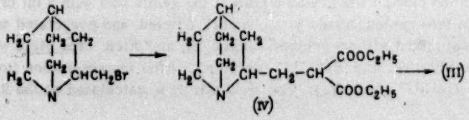
The present paper contains a description of the preparation of one of the homologs of quinuclidine-2-carboxylic acid, namely, β-(quinuclidyl-2)-propionic acid. The acid was synthesized by two routes; from 2-formylquinuclidine, and 2-bromomethylquinuclidine.

The first route was:



2-Formylquinuclidine [2] was condensed with malonic ester in pyridine in the presence of piperidine. The reaction proceeds at room temperature and is accompanied by the formation of only a small amount of by-product. The latter is probably formed by the polymerization of 2-formylquinuclidine. The quinuclidyl-2-methylenemalonic ester (I) formed by the condensation of 2-formylquinuclidine with malonic ester was saponified and partially decarboxylated by boiling with concentrated hydrochloric acid. The β-(quinuclidyl-2)-acrylic acid (II) so formed is easily hydrogenated in the presence of Raney nickel catalyst to form β-(quinuclidyl-2)-propionic acid (III).

The second route was:



2-Bromomethylquinuclidine [3] was condensed with sodium malonate ester in anhydrous butyl alcohol, followed by saponification and decarboxylation of the resultant quinuclidyl-2-methylmalonic ester (IV). The yield of β-(quinuclidyl-2)-propionic acid was 60% by the first method and 20% by the second.

EXPERIMENTAL

1. Quinuclidyl-2-methylenemalonic ester (I). 0.8 g of malonic ester, 3 ml of anhydrous pyridine, and 5 drops of pyridine was added to 0.7 g of freshly distilled 2-formylquinuclidine. The mixture was left to stand in a closed flask 4 days at room temperature (about 15°). The slightly yellow clear solution was evaporated under vacuum at 50°. The residue (1.45 g) was diluted with 5 ml of anhydrous ether, and the ether solution was filtered to remove the white amorphous precipitate which was apparently the polymer of 2-formylquinuclidine. The ether filtrate was evaporated under vacuum and the residue was distilled at 8 mm, b.p. 142-143°, n_D^{20} 1.4821. The yield was 0.93 g (66%) of quinuclidyl-2-methylenemalonic ester.

It is a colorless oily substance with an aromatic odor, easily soluble in the usual organic solvents, insoluble in water.

Found %: C 63.89, 63.66; H 8.08, 7.90; N 4.94, 4.85. $C_{15}H_{23}O_4N$. Calculated %: C 64.04; H 8.18; N 4.98.

β-(Quinuclidyl-2)-acrylic acid (II). A solution of 0.3 g of quinuclidyl-2-methylenemalonic ester in 3 ml of concentrated hydrochloric acid was boiled 6 hours. The reaction mass was then evaporated to dryness, and the residue was mixed with dry acetone, filtered off, and dried. The yield was 0.2 g (90%) of β-(quinuclidyl-2)-acrylic acid hydrochloride.

The substance forms colorless crystals with m.p. 197-198°, is easily soluble in water, with difficulty in alcohol, and is insoluble in ether, acetone, benzene, toluene, and chloroform.

Found %: C 55.23; H 7.47; N 6.43; Cl' 16.61, 16.69. $C_{10}H_{15}O_2N \cdot HCl$. Calculated %: C 55.17; H 7.47; N 6.48; Cl' 16.32.

β-(Quinuclidyl-2)-propionic acid (III). a) To a solution of 0.05 g of β-(quinuclidyl-2)-acrylic acid hydrochloride in 20 ml of distilled water 2.3 ml of 0.1 N caustic soda solution and 1 g of Raney nickel catalyst was added. The mixture was hydrogenated at 17-20° under a pressure of 40-50 mm water column. The theoretical amount of hydrogen (50 ml) was absorbed during half an hour. The catalyst was filtered off and washed with distilled water. The filtrate and the wash waters were treated with 2.3 ml of 0.1 N hydrochloric acid solution and the solution was then evaporated to dryness. The β-(quinuclidyl-2)-propionic acid hydrochloride was extracted from its mixture with sodium chloride by hot anhydrous alcohol. The alcohol solution was evaporated under vacuum. 0.05 g of β-(quinuclidyl-2)-propionic acid was obtained. The yield was quantitative. The substance forms colorless crystals, m.p. 215-216° (decomp.). It is easily soluble in water and hot alcohol, with difficulty in cold alcohol and acetone, and is insoluble in ether, benzene, toluene, and chloroform.

Found %: C 54.87; H 8.35. $C_{10}H_{17}O_2N \cdot HCl$. Calculated %: C 54.67; H 8.20.

b) 0.24 g of sodium was dissolved in 10 ml of anhydrous butyl alcohol. The solution was cooled, and 1.68 g of malonic ester followed by 1 g of 2-bromomethylquinuclidine was added. The reaction mass was heated 20 hours at the boil and then cooled. The precipitate of sodium bromide was filtered off, the filtrate was evaporated under vacuum, the residue was treated with 50% potash solution, and the oil which separated was extracted with ether. The ether extract was dried with potash, the ether was driven off, and the residue was distilled at 35 mm. Two fractions were collected: the 1st fraction, b.p. 90-92°, 1.02 g, was a mixture of residual butyl alcohol, malonic ester, and unreacted 2-bromomethylquinuclidine; the 2nd fraction, b.p. 140-150°, 0.3 g, was the condensation product of 2-bromomethylquinuclidine and sodium malonate ester.

0.3 g of the condensation product was heated 8 hours at the gentle boil with 3 ml of concentrated hydrochloric acid. The solution was then cooled, mixed with charcoal, filtered, and evaporated to dryness in a basin on the water bath. The residue was mixed with dry acetone, filtered off, and dried. The yield was 0.15 g of β-(quinuclidyl-2-)-propionic acid hydrochloride, m.p. 210-211° (decomp.). After reprecipitation from alcohol by means of ether the substance melted at 215-217° (decomp.). The yield was 20%, calculated on the 2-bromomethylquinuclidine.

Found %: Cl' 16.19, 15.80; N 6.28. $C_{10}H_{17}O_2N \cdot HCl$. Calculated %: Cl' 16.17; N 6.37.

Ethyl ester of β-(quinuclidyl-2)-propionic acid. 0.25 g of β-(quinuclidyl-2)-propionic acid hydrochloride was heated 1 hour with 2.5 ml of thionyl chloride at 60-65°. At the end of the reaction, excess thionyl chloride was distilled off under vacuum, and the residue was mixed with 2.5 ml of anhydrous alcohol and heated 2 hours at the boil. The alcohol was distilled off, and the residue was treated with 50% potash solution and extracted with ether. After drying and removal of the ether a residue remained (0.2 g) which was again dissolved in ether. The

ether solution was decolorized by means of charcoal, and methyl iodide was then added. The precipitate of methiodide of the ethyl ester of β-(quinuclidyl-2)-propionic acid was filtered off and reprecipitated from alcohol by means of ether. The yield was 0.15 g of the methiodide of the ethyl ether of β-(quinuclidyl-2)-propionic acid, m.p. 87-89°. Yield 37.5%, calculated on β-(quinuclidyl-2)-propionic acid hydrochloride. It forms colorless crystals, soluble in water and in alcohol, insoluble in ether.

Found %: N 4.11, 3.95; I 35.88. $C_{12}H_{21}O_2N \cdot CH_3I$. Calculated %: N 3.96; I 35.98.

SUMMARY

The synthesis of β-(quinuclidyl-2)-propionic acid has been effected in two ways, from 2-formylquinuclidine and from 2-bromomethylquinuclidine.

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* T.p. = C. B. Translation pagination.

DERIVATIVES OF DIAZINE CARBOXYLIC ACIDS

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The purpose of this work was the synthesis of hydrazides, hydrazones, and certain other derivatives of diazine monocarboxylic acids: pyrazine-2(3)-carboxylic [1], 3-pyridazone-6-carboxylic [2], and pyrimidine-4-carboxylic [3] for the study of their antibacterial action. The methods for the preparation of the first two acids have long been known and fairly well developed, while a catalytic method was developed for the preparation of the last by the reduction of 4-methyl-2,6-dichloropyrimidine to 4-methylpyrimidine in an autoclave at atmospheric pressure in the presence of alkali. The advantage of the catalytic reduction method lies in the small volumes required and the possibility of working without the use of mercury salts, as the 4-methylpyrimidine obtained can be oxidized to pyrimidine-4-carboxylic acid without the need to isolate it. Esters of pyrazine-2-carboxylic and 3-pyridazone-6-carboxylic acids were prepared by boiling alcohol solutions of the acids with concentrated sulfuric acid (the literature contains descriptions of methods with the use of gaseous hydrogen chloride [1,4]). The ethyl ester of pyrimidine-4-carboxylic acid was obtained through its acid chloride. Of the hydrazides of these acids, only pyrazine-2-carboxylic acid hydrazide is described in the literature [5]. The acid hydrazones were easily prepared by brief heating of alcohol solutions of the hydrazides with the corresponding aromatic aldehydes (Table 1). They are substances with high melting points, soluble with difficulty in organic solvents; most hydrazones of 3-pyridazone-6-carboxylic acid do not melt below 330° and are not soluble in organic solvents; therefore analytically pure starting materials had to be used for the preparation of these compounds.

The condensation products of the methyl ester and the acid chloride of pyrazine-2(3)-carboxylic acid [6] with ethylenediamine, monoacetylethylenediamine, o-phenylenediamine, m-nitroaniline, and p-acetaminoaniline were also prepared (Table 2).

All the substances obtained were studied in the Chemotherapy Division of the All-Union Scientific Research Institute for Pharmaceutical Chemistry under the guidance of G. N. Pershin * in relation to their action on various microorganisms (a range of 16 species).

Table 3 shows the bacteriostatic activity of some of the substances to Mycobacterium tuberculosis and pathogenic fungi. The remaining compounds were quite inactive to all types of microorganisms.

EXPERIMENTAL

Methyl ester of pyrazine-2-carboxylic acid. A mixture of 25 g of pyrazine-2-carboxylic acid, 125 ml of anhydrous methyl alcohol, and 5 ml of concentrated sulfuric acid was heated till clear, cooled, and neutralized with hot saturated soda solution. The filtered solution was evaporated to dryness and the residue was extracted with ethyl acetate. After evaporation of the ethyl acetate the residue was distilled under 5-7 mm pressure at 100-104°. The methyl ester of pyrazine-2-carboxylic acid rapidly sets to a crystalline mass with m.p. 62°. Yield was 19.4 g (70%).

Ethyl ester of 3-pyridazone-6-carboxylic acid. A mixture of 5 g of 3-pyridazone-6-carboxylic acid, 25 ml of anhydrous ethyl alcohol, and 0.8 ml of concentrated sulfuric acid was heated till clear. The crystals which separated on cooling were washed with ether and dried in a vacuum desiccator. The yield was 4.2 g (70%) of the ethyl ester of 3-pyridazone-6-carboxylic acid; this is a snow-white crystalline substance, m.p. 123-125°.

Hydrazide of 3-pyridazone-6-carboxylic acid. 3.6 g of hydrazine hydrate in 7 ml of alcohol was added to a solution of 6 g of the ethyl ester of 3-pyridazone-6-carboxylic acid in 25 ml of alcohol. The mixture was heated 10 minutes, the precipitate which formed was filtered off and washed with alcohol and ether. The yield was 5.3 g of 3-pyridazone-6-carboxylic acid hydrazide, easily soluble in hot water, soluble with difficulty in the usual organic solvents; it does not melt at 330°.

Found %: C 39.17; H 4.04. $C_5H_6O_2N_4$. Calculated %: C 38.96; H 3.89.

* The investigations were carried out by O. O. Makeeva and S. N. Milovanova.

TABLE 1

Hydrazides of acids	Aldehydes	Solvents	Yield of hydrazone (%)	M.p. of hydrazone	Formula of hydrazone	Found (%)			Calculated (%)		
						C	H	N	C	H	N
Pyrazine-2-carboxylic	4-Hydroxy-3-methoxybenzaldehyde	Anhydrous alcohol	86.5	214-242°	$C_{13}H_{12}O_3N_4$	56.6	4.56	–	57.5	4.42	–
	p-Hydroxybenzaldehyde		97	290-291°	$C_{13}H_{10}O_2N_4$	59.29	3.90	–	59.50	4.13	–
	3,4-Methoxy-2-carboxybenzaldehyde		75	217-218°	$C_{15}H_4O_5N_4$	54.88	4.40	–	54.54	4.24	–
3-Pyridazone-6-carboxylic	p-Hydroxybenzaldehyde	Aqueous alcohol	80	•	$C_{12}H_{10}O_3N_4$	–	–	21.64	–	–	21.71
	4-Acetaminobenzaldehyde		77.5	330°	$C_{14}H_{13}O_3N_5$	56.07	4.33	–	56.18	4.34	–
	4-Hydroxy-3-methoxybenzaldehyde		80.6	296-298°	$C_{13}H_{12}O_4N_4$	54.16	4.13	–	54.16	4.16	–
	4-Dimethylaminobenzaldehyde		84	285°	$C_{14}H_{15}O_2N_5$	58.29	5.41	–	58.94	5.96	–
Pyrimidine-4-carboxylic	4-Hydroxy-3-methoxybenzaldehyde	Water	–	252-253°	$C_{13}H_{12}O_3N_4$	56.93	4.68	19.68	57.3	4.42	20.6
	4-Hydroxybenzaldehyde		–	285-286°	$C_{12}H_{10}O_2N_4$	59.29	4.00	23.02	59.6	4.13	23.1
	4-Acetaminobenzaldehyde		–	288-289°	$C_{14}H_{13}O_2N_5$	–	–	21.44	–	–	24.7

• Does not melt at 335°

TABLE 2

Substituted Amides of Pyrazine-2-carboxylic Acid

Starting Substances	Solvent	Yield of amide (%)	M.p. of amide	Formula of amide	Found (%)			Calculated (%)		
					C	H	N	C	H	N
Methyl ester of pyrazine-2-carboxylic acid and monoacetylethylenediamine	Anhydrous alcohol	38	187-188°	$C_9H_{12}O_2N_4$	52.06	5.61	28.86	51.92	5.76	26.92
Acid chloride of pyrazine-2-carboxylic acid and o-phenylenediamine	Ethyl acetate	–	199-200° •	$C_{11}H_{10}ON_4$	61.3	2.05	26.18	61.68	4.67	26.16
Acid chloride of pyrazine-2-carboxylic acid and m-nitroaniline	Ethyl acetate	79	176-177°	$C_{11}H_8O_3N_4$	53.9	3.43	23.23	54.09	3.29	22.95
Acid chloride of pyrazine-2-carboxylic acid and p-acetaminoaniline	Ethyl acetate	88	229-230°	$C_{13}H_{12}O_2N_4$	–	–	21.98	–	–	–

• acetyl deriv. m.p. 105-107°

TABLE 3

Substance	Activity in vitro, in dilutions:		
	Mycobacterium tuberculosis		
	"Academy" strain		H37 Rv strain
	Without serum	With serum	With serum
Pyrazine-2-carboxylic acid hydrazide	1 : 64000	1 : 8000	1 : 64000
Pyrazine-2-carboxylic acid 4-hydroxy-3-methoxybenzal-hydrazide	1 : 4000	1 : 1000	1 : 16000
Pyrazine-2-carboxylic acid 4-hydroxybenzalhydrazide	1 : 1000		1 : 6000
Pyrazine-2-carboxylic acid 3,4-methoxy-2-carboxybenz-alhydrazide	1 : 4000	1 : 2000	1 : 16000
Pyrimidine-4-carboxylic acid hydrazide	1 : 8000	1 : 8000	1 : 16000
	Pathogenic fungi		
	microsporon	trichophyton	achorion
Pyrazine-2-carboxylic acid o-aminophenylamide	1 : 1000	1 : 2000	1 : 2000

4-Methylpyrimidine. A mixture of 15 g of 4-methyl-2,6-dichloropyrimidine, 25 ml of water, 12 g of KOH, and 1.5 g of Raney nickel catalyst was hydrogenated in an autoclave at 90 atmospheres at room temperature. The catalyst was filtered off, the filtrate was diluted to 200 ml with water, and the 4-methylpyrimidine content was determined by titration with mercuric chloride. The yield of 4-methylpyrimidine was 3.9 g (45%).

Pyrimidine-4-carboxylic acid. To a solution of 3.9 g of 4-methylpyrimidine in 200 ml of water heated to boiling, a solution of 50 g of $KMnO_4$ in 400 ml of water was added during 4 hours with stirring. When the solution was decolorized, the MnO_2 was filtered off and the filtrate evaporated to 50 ml. The aqueous distillate contained unoxidized 4-methylpyrimidine. The residue was acidified first with 50% HNO_3, and then dropwise with concentrated HNO_3. The finely granular precipitate of pyrimidine-4-carboxylic acid was filtered off, washed with water, and dried. Yield 2.25 g (54%). M.p. 238-240°.

Ethyl ester of pyrimidine-4-carboxylic acid. A mixture of 2.25 g of pyrimidine-4-carboxylic acid, 25 ml of benzene, and 2 ml of freshly distilled thionyl chloride was boiled 40 minutes, then excess of thionyl chloride was driven off under vacuum and 12 ml of anhydrous ethyl alcohol was added to the residue. The solution was boiled 2 hours, and then excess alcohol was removed, the residue treated with soda solution, extracted with ether, and the ether extract dried with sodium sulfate. After removal of ether, the ethyl ester of pyrimidine-4-carboxylic acid was distilled at 155-160° (88 mm). The liquid rapidly set into crystals with m.p. 37-39°. Yield 2.4 g (84.6%).

Found %: C 55.5; H 5.46. $C_7H_8O_2N_2$. Calculated %: C 55.2; H 5.26.

Hydrazide of pyrimidine-4-carboxylic acid. A mixture of 0.3 g of the ethyl ester of pyrimidine-4-carboxylic acid and 0.2 g of hydrazine hydrate was ground in a mortar; heat was evolved. After cooling, the precipitate was filtered off, washed with alcohol, and recrystallized from alcohol. The yield of pyrimidine-4-carboxylic acid hydrazide, m.p. 147-147.5°, was 0.25 g (92%).

Found %: C 43.74; H 4.49; N 40.16. $C_5H_6ON_4$. Calculated %: C 43.5; H 4.35; N 40.6.

Dipyrazinyldiaminoethane. A solution of 5 g of ethylenediamine in 5 ml of anhydrous methyl alcohol was added to a hot solution of 3 g of the methyl ester of pyrazinecarboxylic acid in 10 ml of anhydrous methyl alcohol, and the mixture was boiled a short time. The fine crystalline precipitate was separated off and thoroughly washed with alcohol. Yield 1.8 g. After recrystallization from 50% acetic acid, m.p. 296-297°. Dipyrazinyldiaminoethane dissolves in dioxane with difficulty, and is almost insoluble in alcohol and in acetone. It is not changed when boiled with acetic anhydride.

Found %: C 53.05; H 4.37; N 30.76. $C_{12}H_{12}O_2N_6$. Calculated %: C 52.94; H 4.41; N 30.88.

SUMMARY

1. The hydrazones of pyrazine-2-carboxylic acid with p-hydroxybenzaldehyde, 4-hydroxy-3-methoxybenzaldehyde, and 3,4-methoxy-2-carboxybenzaldehyde, and also the condensation products of the methyl ester and the acid chloride of pyrazine-2-carboxylic acid with ethylenediamine, monoacetylethylenediamine, o-phenylenediamine, m-nitroaniline, and p-acetaminoaniline, have been prepared.

2. The hydrazide of 3-pyridazone-6-carboxylic acid was prepared, and from it the corresponding hydrazones with p-hydroxybenzaldehyde, 4-acetaminobenzaldehyde, 4-hydroxy-3-methoxybenzaldehyde, and 4-dimethylaminobenzaldehyde were obtained.

3. A new method for the preparation of 4-methylpyrimidine by the catalytic reduction of 4-methyl-2,6-dichloropyrimidine in the presence of alkali has been developed.

4. The ethyl ester and the hydrazide of pyrimidine-4-carboxylic acid, and also the corresponding hydrazones with 4-hydroxybenzaldehyde, 4-acetaminobenzaldehyde, and 4-hydroxy-3-methoxybenzaldehyde have been prepared.

5. The compounds obtained do not have any antibacterial action with the exception of five substances which showed slight activity against the tuberculosis bacillus, and one against pathogenic fungi.

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INVESTIGATIONS IN THE IMIDAZOLE SERIES

II. 4(5)-PHENYLIMIDAZOLYL-2-ALKYL(ARYL) SULFONES AND SULFOXIDES

P. N. Kochergin and M. N. Shchukina

No sulfones derived from imidazole are described in the literature; only one representative of the sulfoxides is known [1]. Nevertheless, synthesis of imidazolyl sulfoxides and sulfones is not only of interest from the chemical standpoint, but provides a possibility for testing their antibacterial activity, in particular against the tuberculosis bacillus, as sulfones of the aromatic [2] and heterocyclic series [3] have antitubercular action. The starting materials for the preparation of sulfoxides and sulfones were the 4(5)phenylimidiazolyl-2-alkyl(aryl) sulfides synthesized by us [4]. The oxidizing agent used was 20-27% hydrogen peroxide in glacial acetic acid. Sulfoxides or sulfones are formed, in accordance with the amount of oxidizing agent. The oxidation of imidazolyl sulfides to sulfones proceeds stepwise, through the formation of sulfoxides. Thus, the action of an equimolecular quantity of hydrogen peroxide on 4(5)-phenyl-2-isoamyl- and 4(5)-phenyl-2-n-hexylmercaptoimidazoles at room temperature yielded the corresponding sulfoxides (the yield of the former was 98%), while the action of 2 moles of hydrogen peroxide on 1 mole of 4(5)-phenylimidazolyl-2-alkyl(aryl) sulfides in the same conditions (15-45°) leads to the formation of sulfones (yield 70-94%). 4(5)-Phenylimidazolyl-2-isoamyl sulfoxide is converted into the sulfone (90% yield) when oxidized by an equimolar amount of hydrogen peroxide at room temperature. In contrast to the other sulfides studied, when 1-ethyl--4-phenyl-2-ethylmercaptoimidazole was oxidized by an equimolar amount of hydrogen peroxide at room temperature, the sulfoxide was not obtained (the starting material was isolated in good yield), while the action of 2 moles of hydrogen peroxide on 1 mole of the sulfide yielded not the sulfone but the sulfoxide. This sulfoxide was not oxidized to the sulfone when heated to 100° in 10% nitric acid.

The sulfones obtained, containing a nitro group in the benzene nucleus, were reduced to the corresponding amines. 4(5)-Phenylimidoazolyl-2-p-nitrophenyl sulfone was reduced by means of hydrogen sulfide in alcoholic ammonia solution [5], while 4(5)-p-nitrophenylimidazolyl-2-isoamyl sulfone was reduced by hydrogen in the presence of Raney nickel catalyst at room temperature and atmospheric pressure.

The imidazolyl-2-alkyl(aryl) sulfones are crystalline substances with weaker basic properties than the corresponding sulfides or sulfoxides; their hydrochlorides are hydrolyzed even in alcohol solutions. For example, 4(5)--phenylimidazolyl-2-p-aminophenyl sulfone and 4(5)-p-nitrophenylimidazolyl-2-isoamyl sulfone are precipitated unchanged from a hot solution of hydrogen chloride in alcohol. Consequently, the presence of a sulfonylalkyl (aryl) group in position two greatly weakens the basic properties of the imidazole nucleus.

The imidazolyl-2-alkyl(aryl) sulfones, and 4(5)-phenylimidazolyl-2-isoamyl sulfoxide hydrochloride, were tested for antibacterial activity in the Chemotherapy Division of the All-Union Scientific Research Institute for Pharmaceutical Chemistry (range of 16 species of microorganisms)*. The table shows the dilutions at which the compounds completely inhibit the in vitro growth of the microorganisms (9 species). All the compounds proved inactive to Staphylococcus aureus, the enteric, typhoid, Flechsner's dysentery, and pyocyaneus bacilli, to Proteus vulgaris and anthracoid spores, with the exception of 4(5)-phenylimidoazolyl-2-isoamyl sulfoxide hydrochloride, which was active against Staphylococcus aureus (1:4000), and 4(5)-phenylimidazolyl-2-n-hexyl sulfone, against anthracoid spores (1:8000). It was found that the sulfones derived from imidazole are less active against the tuberculosis bacillus than the corresponding sulfides [4]. 4(5)-p-Nitrophenylimidazolyl-2-isoamyl sulfone and 4(5)-phenylimidazolyl--2-p-nitrophenyl sulfone are inactive. A comparison of the antitubercular activity of 4(5)-phenylimidazolyl-2-isoamyl sulfide [4] and the corresponding sulfoxide and sulfone shows that the sulfoxide is the most active, but its activity also decreases sharply in the presence of normal horse serum.

* The investigations were carried out by S. N. Milovanova, O. O. Makeeva, and A. A. Mikerina under the guidance of G. N. Pershin.

EXPERIMENTAL

I. 4(5)-Phenylimidazolyl-2-methyl sulfone. 0.68 ml of 27% aqueous hydrogen peroxide was added to 0.5 g of 4(5)-phenyl-2-methylmercaptoimidazole in 4 ml of glacial acetic acid, and the solution was left 100 hours at 25-30°. The colorless solution was then neutralized by a saturated solution of sodium bicarbonate, and the white crystalline precipitate which formed was filtered off, washed with water, and dried. The yield was 0.42 g (72%) of substance with m.p. 142-145°; after recrystallization from 30% alcohol the m.p. was 149-150°. It forms colorless crystals, easily soluble in most organic solvents and in mineral acids, soluble with difficulty in ether, insoluble in cold water, petroleum ether, and cold dilute alkali.

Found %: C 54.24; H 4.48; N 12.61. $C_{10}H_{10}O_2N_2S$. Calculated %: C 54.01; H 4.53; N 12.61.

II. 4(5)-Phenylimidazolyl-2-ethyl sulfone. This was prepared analogously to (I) from 0.6 g of 4(5)-phenyl-2-ethylmercaptoimidazole by oxidation with 0.77 ml of 27.12% hydrogen peroxide in 4 ml of glacial acetic acid (25-30°; 48 hours). The yield of substance with m.p. 125-126° was 0.48 g (70%). After recrystallization from toluene or alcohol it forms colorless needles, m.p. 127.5-128°; it is soluble in most organic solvents and mineral acids and insoluble in water, carbon tetrachloride, petroleum ether, and cold caustic soda solution.

Found %: C 55.91; H 5.05; N 11.98; S 13.60. $C_{11}H_{12}O_2N_2S$. Calculated %: C 55.90; H 5.11; N 11.86; S 13.57.

III. 4(5)-Phenylimidazolyl-2-n-propyl sulfone. This was prepared analogously to (I) from 0.3 g of 4(5)-phenyl-2-n-propylmercaptoimidazole and 0.4 ml of 27.12% hydrogen peroxide in 1 ml of glacial acetic acid (15-18°; 48 hours). The yield of substance with m.p. 109-111° was 0.3 g; after recrystallization from 60-70% alcohol it forms colorless needles, m.p. 142-143°; solubility similar to that of (I).

Found %: C 57.31; H 5.77; N 11.03; S 13.14. $C_{12}H_{14}O_2N_2S$. Calculated %: C 57.56; H 5.64; N 11.19; S 12.81.

IV. 4(5)-Phenylimidazolyl-2-n-butyl sulfone. This was prepared analogously to (I) from 0.5 g of 4(5)-phenyl-2-n-butylmercaptoimidazole hydrochloride and 0.5 ml of 27.12% hydrogen peroxide in 66% acetic acid. The yield of substance with m.p. 142-145° was 0.42 g; after recrystallization from alcohol it forms long needles, m.p. 153-154°; solubility similar to that of (II).

Found %: C 58.92; H 6.15; N 10.80; S 11.97. $C_{13}H_{16}O_2N_2S$. Calculated %: C 59.05; H 6.10; N 10.60; S 12.13.

V. 4(5)-Phenylimidazolyl-2-isoamyl sulfoxide. 3.40 ml of 27.25% hydrogen peroxide was added to 7.9 g of 4(5)-phenyl-2-isoamylmercaptoimidazole in 50 ml of glacial acetic acid, and the solution was left 24 hours at room temperature and then evaporated to dryness under vacuum. The white crystalline residue was washed with ether and dried. The yield was 7.3 g (98.8%) of substance with m.p. 149-150°. The hydrochloride of 4(5)-phenylimidazolyl-2-isoamyl sulfoxide forms colorless leaflets from alcohol, m.p. 158-159° (decomp.); it is soluble in alcohol and acetone, and soluble with difficulty in water.

Found %: C 56.32; H 6.46; N 9.27; S 10.57; Cl 12.01. $C_{14}H_{19}ON_2SCl$. Calculated %: C 56.25; H 6.41; N 9.38; S 10.73; Cl 11.87.

The hydrochloride was dissolved in alcohol and neutralized by sodium bicarbonate to yield the base, 4(5)-phenylimidazolyl-2-isoamyl sulfoxide, a thick colorless oily liquid, soluble in most organic solvents, insoluble in water and in cold alkali solution; it decomposes when distilled under vacuum.

VI. 4(5)-Phenylimidazolyl-2-isoamyl sulfone. 1. This was prepared analogously to (V) from 3 g of 4(5)-phenyl-2-isoamylmercaptoimidazole hydrochloride by oxidation by means of 2.9 ml of 27% hydrogen peroxide in 50 ml of glacial acetic acid (40-45°; 48 hours). After evaporation of the solvent under vacuum, the residue was treated with sodium bicarbonate solution, and the precipitate was filtered off and dried. The yield was 2.7 g of substance with m.p. 138°; after recrystallization from alcohol it forms long needles m.p. 150-151°; solubility analogous to (I).

2. 0.4 ml of 20% hydrogen peroxide was added to 0.5 g of 4(5)-phenylimidazolyl-2-isoamyl sulfoxide hydrochloride in 5 ml of glacial acetic acid; the solution was left 72 hours at room temperature, then evaporated to a small volume and neutralized by sodium bicarbonate solution. The white crystalline precipitate was filtered off, washed with water, and dried. The yield was 0.41 g of substance with m.p. 143-147° (90%). After recrystallization from alcohol the substance melted at 150-151° and gave no melting point depression with 4(5)-phenylimidazolyl-

-2-isoamyl sulfone prepared by Method (I).

Found %: C 60.40; H 6.51; N 10.37; S 11.95. $C_{14}H_{18}O_2N_2S$. Calculated %: C 60.39; H 6.52; N 10.06; S 11.52.

VII. 4(5)-Phenylimidoazolyl-2-n-hexyl sulfoxide. This was prepared analogously to (V) from 0.8 g of 4(5)-phenyl-2-n-hexylmercaptoimidazole and 0.5 ml of 20% hydrogen peroxide in 20 ml of glacial acetic acid (15-18°; 48 hours). After removal of the solvent under vacuum, sodium bicarbonate solution was added and the oily substance was extracted with ether. The ether solution was dried over magnesium sulfate and an ether solution of picric acid was added. The yellow precipitate was filtered off and recrystallized from alcohol. The result was picrate of 4(5)-phenylimidazolyl-2-n-hexyl sulfoxide, m.p. 149-150°.

Found %: C 49.86; H 4.37; N 13.68; S 6.13. $C_{21}H_{23}O_8N_5S$. Calculated %: C 49.87; H 4.58; N 13.86; S 6.34.

The free base, 4(5)-phenylimidazolyl-2-n-hexyl sulfoxide, is a noncrystallizing oil, soluble in most organic solvents, insoluble in water.

VIII. 4(5)-Phenylimidazolyl-2-n-hexyl sulfone. This was prepared analogously to (I) from 0.4 g of 4(5)--phenyl-2-n-hexylmercaptoimidazole hydrochloride and 0.37 ml of 27.12% hydrogen peroxide in 6 ml of 66% acetic acid (15-18°; 48 hours). The yield of substance with m.p. 95-97° was 0.31 g (79.5%); after recrystallization from alcohol it forms colorless needles, m.p. 102-103°; the solubility is similar to that of (II).

Found %: C 61.79; H 7.08; N 9.80; S 10.94. $C_{15}H_{20}O_2N_2S$. Calculated %: C 61.60; H 6.90; N 9.58; S 10.97.

IX. 4(5)-Phenylimidazolyl-2-p-nitrophenyl sulfone. 3.6 ml of 27.25% hydrogen peroxide was added to 4.0 g of 4(5)-phenyl-2-p-nitrophenylmercaptoimidazole in 30 ml of glacial acetic acid; the solution was left 45 hours at 40-45°, and then evaporated to a small volume under vacuum; the yellow crystalline precipitate which separated after cooling was filtered off, washed with a small amount of acetic acid, and dried. The yield was 4.0 g of substance with m.p. 169-172°. Evaporation of the mother liquor yielded a further 0.15 g of substance with m.p. 168-170° (total yield 93.9%). 4(5)-Phenylimidazolyl-2-p-nitrophenyl suflone forms pale yellow prisms from glacial acetic acid, m.p. 180-181.5°; it is soluble in most of the common organic solvents, dissolves with difficulty in hydrochloric acid, and is insoluble in water, petroleum ether, carbon tetrachloride, and cold alkali solutions.

Found %: C 54.80; H 3.64; N 12.67; S 9.93. $C_{15}H_{11}O_4N_3S$. Calculated %: C 54.69; H 3.36; N 12.76; S 9.74.

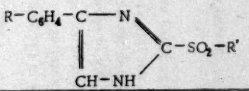
X. 4(5)-Phenylimidazolyl-2-p-aminophenyl sulfone. To a solution of 4.6 g of 4(5)-phenylimidazolyl-2--p-nitrophenyl sulfone in 200 ml of alcohol, 26 ml of aqueous ammonia solution (d 0.92) was added, and a stream of hydrogen sulfide was passed 5 hours at room temperature. The solution was then heated 1 hour at the boil and evaporated to dryness under vacuum; the residue was treated with boiling acetone, the solution was filtered, and evaporated to dryness under vacuum. The yield was 3.0 g (72.1%) of substance with m.p. 232-234° (decomp.). It forms colorless long prisms (from 70% alcohol), m.p. 240.5-241° (decomp.); soluble in dioxane, glacial acetic acid, alcohol, acetone, and hydrochloric acid on warming; insoluble in water, benzene, toluene, ether, chloroform, carbon tetrachloride, ethyl acetate, ligroine, and cold caustic soda solution. From hot hydrochloric acid the base itself, m.p. 240.5-241°, and not the hydrochloride, is precipitated.

Found %: C 59.99; H 4.35; N 14.21; S 10.84. $C_{15}H_{13}O_2N_3S$. Calculated %: C 60.17; H 4.38; N 14.04; S 10.71.

XI. 4(5)-p-Nitrophenylimidazolyl-2-isoamyl sulfone. To 2.6 g of 4(5)-p-nitrophenyl-2-isoamylmercaptoimidazole hydrochloride in 20 ml of glacial acetic acid 2.1 ml of 27.25% hydrogen peroxide was added and the solution was left 24 hours at 40-45°. The yellow crystalline precipitate which formed was filtered off and dried; the yield was 1.8 g of substance with m.p. 171-173°. Evaporation of the mother liquor yielded a further 0.5 g of substance with m.p. 171-172° (total yield 89.9%). It forms yellow prisms (from glacial acetic acid), m.p. 178-178.5°; soluble in most organic solvents, insoluble in water and cold dilute alkali. From hot solution in concentrated hydrochloric acid the unchanged base with m.p. 178-178.5°, and not the hydrochloride, is precipitated.

Found %: C 52.12; H 5.15; N 12.96; S 10.00. $C_{14}H_{17}O_4N_3S$. Calculated %: C 51.98; H 5.30; N 13.00; S 9.92.

TABLE

Antibacterial Activity of Compounds with the General Formula 

R	R'	Activity against organisms								
		hemolytic streptococcus	pneumococcus	diphtheria bacillus (strain PW_8)	human tuberculosis	avian tuberculosis	acid-resistant saprophyte B_5	microsporon	trichophyton	achorion
NH_2 *	C_6H_{11}	0 **	1:4000	0	1:4000	1:2000	1:2000	0	1:1000	1:1000
H	CH_3	0	0	0	1:1000	1:1000	0	0	0	0
H	C_3H_5	0	0	0	1:1000	1:1000	1:1000	0	0	0
H	C_5H_7	1:2000	1:2000	1:2000	1:4000	1:2000	0	1:1000	1:2000	1:1000
H	C_4H_9	0	0	0	1:2000	0	0	0	1:1000	1:1000
H	C_5H_{11}	0	0	0	1:2000	0	0	1:1000	1:1000	1:1000
H	C_5H_{11} ***	1:2000	1:2000	0	1:512000 ****	1:16000	1:16000	1:16000	1:16000	1:16000
H	C_6H_{13}	1:4000	0	1:2000	1:128000	1:32000	1:16000	1:16000	1:16000	1:32000
H	$C_6H_4NH_2$	0	0	0	1:1000	1:8000	1:1000	1:2000	0	0

* Tested as the hydrochloride.

** 0 = absence of activity.

*** 4(5)-Phenylimidazolyl-2-isoamyl sulfoxide hydrochloride.

**** In the presence of normal horse serum (1 : 16000).

XII. 4(5)-Aminophenylimidazolyl-2-isoamyl sulfone. 2.8 g of moist Raney nickel catalyst was added to 0.7 g of 4(5)-p-nitrophenylimidazolyl-2-isoamyl sulfone in 100 ml of alcohol. The reduction took place at room temperature and atmospheric pressure, and was complete in 1 hour, when 126 ml of hydrogen had been absorbed. The catalyst was filtered off and washed with alcohol, the mother liquor and wash alcohol were evaporated, and the residue was dried in a vacuum desiccator. The yield was 0.6 g (95.7%) of substance with m.p. 150-155° (decomp.). The substance was converted into the hydrochloride; this was dissolved in alcohol and dry sodium bicarbonate was added to liberate the base, 4(5)-p-aminophenylimidazolyl-2-isoamyl sulfone, which forms long colorless prisms from alcohol, m.p. 164-165°, soluble in most organic solvents and mineral acids, insoluble in water, ligroine, carbon tetrachloride, and cold alkali solutions.

Found %: C 57.55; H 6.43; N 13.87; S 11.07. $C_{14}H_{19}O_2N_3S$. Calculated %: C 57.29; H 6.53; N 14.33; S 10.93.

The hydrochloride forms colorless leaflets (from alcohol), m.p. 242-246° (decomp. in sealed capillary).

Found %: Cl 11.09. $C_{14}H_{20}O_2N_3SCl$. Calculated %: Cl 10.75.

XIII. 1-Ethyl-4-phenylimidazolyl-2-ethyl sulfoxide. 4.6 ml of 27% hydrogen peroxide was added to a solution of 3.85 g of 1-ethyl-4-phenyl-2-ethylmercaptoimidazole in 25 ml of glacial acetic acid, and the solution was left to stand 48 hours at 40-50°. The acetic acid was distilled off under vacuum, sodium bicarbonate solution was added to the residue, and the oil which separated was extracted with chloroform. The chloroform solution was dried over sodium sulfate, filtered, and evaporated to dryness under vacuum. The oil which remained was dried in a vacuum desiccator. The yield was 3.3 g of a slightly brownish oily substance, soluble in most organic solvents, insoluble in water. The picrate of 1-ethyl-4-phenylimidazolyl-2-ethyl sulfoxide was prepared for analysis, in the form of long needles from alcohol, m.p. 151° (decomp.).

Found %: C 47.76; H 3.88; N 14.38; S 6.77. $C_{19}H_{19}O_8N_5S$. Calculated %: C 47.77; H 4.01; N 14.68; S 6.72.

SUMMARY

1. A series of 4(5)-phenylimidazolyl-2-alkyl(aryl) sulfones and sulfoxides was prepared.

2. The mechanism of the oxidation of imidazolyalkyl(aryl) sulfides to sulfones was studied.

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SYNTHESIS OF AROMATIC ARSENOORGANIC COMPOUNDS BY WAY OF DOUBLE DIAZONIUM SALTS

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The method discovered by A. N. Nesmeyanov in 1929 [1] for the synthesis of aromatic mercuroorganic compounds by way of the double diazonium salts was later extended to the synthesis of metalorganic compounds of tin, lead, thallium, antimony, and bismuth.

With the aim of developing a preparative method for the synthesis of arsenoorganic compounds, we made a detailed study of the decomposition of double diazonium salts of ferric chloride and zinc chloride by means of powdered iron in acetone in the cold in the presence of arsenic trichloride and phenyldichloroarsine*. By means of this reaction we synthesized arsenoorganic compounds of various types, containing the following aromatic radicals: phenyl, p-tolyl, p-chlorophenyl, p-bromophenyl, 2,4,6-tribromophenyl, p-methoxyphenyl, and p-ethoxyphenyl.

The general method for carrying out the reaction consists of the gradual addition of the powdered metal used as reducing agent to suspensions (in the case of zinc salts) or solutions (in the case of iron salts) of the double salts in a small volume of dry acetone in which arsenic trichloride or an aryldichloroarsine is dissolved, cooled to −20° and thoroughly stirred by means of a centrifugal stirrer. It is also possible to reverse the order for the addition of the reagents, the double salt being added to a suspension of powdered iron or zinc. The reactions usually proceed vigorously; evolution of nitrogen ceases after 1-1.5 hours. The rate of mixing of the reagents is so chosen that the temperature of the reaction mixture does not rise above 5-7°, as otherwise resin formation is intensified.

Separation of the arsenoorganic compounds formed was usually carried out after alkaline hydrolysis to the corresponding oxides, dihydroxides, or acids. In some instances vacuum distillation (without the use of hydrolysis) was used to isolate and separate the reaction products. Distillation in the form of chlorides proved, for example, the only suitable method for mixed disubstituted derivatives (with two different radicals joined to the arsenic), the hydrolysis products of which are usually very viscous oils which resist purification. Some mixed derivatives of trivalent arsenic were oxidized to the corresponding acids for identification.

The results of the experiments are shown in Tables 1 and 2. As the results in Table 1 show, in all the experiments on arylation of arsenic trichloride the reaction resulted in the formation of a mixture of two substances of the type $ArAsX_2$, Ar_2AsX, Ar_3As or Ar_3AsX_2, where X = Cl, OH, $\frac{1}{2}$ O. In one instance a diarylarsinic acid was isolated.

The decomposition of double diazonium salts of ferric chloride and zinc chloride in the presence of $AsCl_3$ apparently occurs according to the following schemes:

$$ArN_2Cl \cdot FeCl_3 + AsCl_3 + Fe \rightarrow ArAsCl_2 + N_2 + FeCl_2 + FeCl_3,$$
$$2ArN_2Cl \cdot FeCl_3 + AsCl_3 + 2Fe \rightarrow Ar_2AsCl + 2N_2 + 2FeCl_2 + 2FeCl_3,$$
$$3ArN_2Cl \cdot FeCl_3 + AsCl_3 + 3Fe \rightarrow Ar_3As + 3N_2 + 3FeCl_2 + 3FeCl_3,$$
$$3ArN_2Cl \cdot FeCl_3 + AsCl_3 + 2Fe \rightarrow Ar_3AsCl_2 + 3N_2 + 2FeCl_2 + 3FeCl_3.$$

The arylation of aryldichloroarsines (Table 2) probably follows the equations:

$$(Ar'N_2Cl)_2 \cdot ZnCl_2 + 2ArAsCl_2 + 2Fe \rightarrow 2ArAr'AsCl + 2N_2 + ZnCl_2 + 2FeCl_2,$$
$$(Ar'N_2Cl)_2 \cdot ZnCl_2 + ArAsCl_2 + 2Fe \rightarrow ArAr'_2As + 2N_2 + ZnCl_2 + 2FeCl_2,$$
$$(Ar'N_2Cl)_2 \cdot ZnCl_2 + ArAsCl_2 + Fe \rightarrow ArAr'_2AsCl_2 + 2N_2 + ZnCl_2 + FeCl_2.$$

In the arylation of $ArAsCl_2$, in all the cases studied, only one final arsenoorganic compound is formed (of of type $ArAr'AsZ$, $ArAr'_2As$ or $ArAr'_2AsX_2$).

* The literature contains some limited data on the synthesis of arsenoorganic compounds by way of the double diazonium salts [2,3] or the solid aryl diazonium chlorides [4].

TABLE 1

Substances Formed by Arylation of Arsenic Trichloride by Double Diazonium Salts of Zinc Chloride and Ferric Chloride

Experiment No.	Double salt	Moles of double salt to moles of $AsCl_3$	g-atoms of Fe to moles of double salt	$ArAsX_2$								Ar_2AsX and		
				formula	Yield (%) on $AsCl_3$	Yield (%) on the double salt	melting point	% C calculated	% C found	% H calculated	% H found	formula	Yield (%) on $AsCl_3$	Yield (%) on the double salt
1	$C_6H_5N_2Cl \cdot FeCl_3$	1/1	5.7/1	—	—	—	—	—	—	—	—		19	38
2	$C_6H_5N_2Cl \cdot FeCl_3$	1.4/1	4/1	—	—	—	—	—	—	—	—	$[(C_6H_5)_2As]_2O$	15	30
3	$C_6H_5N_2Cl \cdot FeCl_3$	2/1	3/1	—	—	—	—	—	—	—	—		3	3
4	$(C_6H_5N_2Cl)_2 \cdot ZnCl_2$	1/1	4/1	—	—	—	—	—	—	—	—	$(C_6H_5)_3As$	29	43
5 *	$(C_6H_5N_2Cl)_2 \cdot ZnCl_2$	2/1	5.3/1	—	—	—	—	—	—	—	—	—	—	—
6	$(C_6H_5N_2Cl)_2 \cdot ZnCl_2$	1/1	6/1	—	—	—	—	—	—	—	—		20	20
7 **	$(C_6H_5N_2Cl)_2 \cdot ZnCl_2$	1/1	6/1	—	—	—	—	—	—	—	—	$[(C_6H_5)_2As]_2O$	12	12
8	$(C_6H_5N_2Cl)_2 \cdot ZnCl_2$	1/1.5	2/1	C_6H_5AsO	11	8.5	121—122°	—	—	—	—		23	35
9	$(C_6H_5N_2Cl)_2 \cdot ZnCl_2$	1/1.5	3/1	C_6H_5AsO	5.5	4.0	120	—	—	—	—		12	18
10	$(p\text{-}ClC_6H_4N_2Cl)_2 \cdot ZnCl_2$	1/1.5	3/1	ClC_6H_4AsO	16.5	12.5	186—187	35.56	36.20, 36.03	1.99	1.74, 1.76	$[(ClC_6H_4)_2As]_2O$ ****	24	36
11 *	$(p\text{-}ClC_6H_4N_2Cl)_2 \cdot ZnCl_2$	1.3/1	3/1	—	—	—	—	—	—	—	—		9	6
12***	$(p\text{-}CH_3C_6H_4N_2Cl)_2 \cdot ZnCl_2$	1/1	3/1	$CH_3C_6H_4AsO$	9	4.5	153—154	46.19	45.32, 45.34	3.88	4.03, 4.15	$(CH_3C_6H_4)_3As$	28.5	42.5
13	$(p\text{-}BrC_6H_4N_2Cl)_2 \cdot ZnCl_2$	1/1	2/1	BrC_6H_4AsO	13	6.5	139—142	29.18	29.22, 29.06	1.63	1.64, 1.82	—	—	—
14	$(2,4,6\text{-}Br_3C_6H_2N_2Cl)_2 \cdot ZnCl_2$	1/2	4/1	—	—	—	—	—	—	—	—		33	66
15 *	$(2,4,6\text{-}Br_3C_6H_2N_2Cl)_2 \cdot ZnCl_2$	1/1	4/1	—	—	—	—	—	—	—	—	$[(Br_3C_6H_2)_2As]_2$ ****	11	11

* Half the amount of the double salt was added after the reaction and after separation of the unreacted iron.

** Volume of solvent was three times that in the preceding experiment.

*** The reaction products were separated after reduction of the mixture by sulfur dioxide.

**** Substance described for the first time.

***** Passes into oxide at 119°.

(Decomposition with powdered iron or zinc in acetone)

Ar_3As					Ar_3AsX_2 and Ar_2AsX_3								Total yield of arseno-organic compounds (%)	
	% C		% H			Yield (%)			% C		% H			
melting point	calculated	found	calculated	found	formula	on $AsCl_3$	on the double salt	melting point	calculated	found	calculated	found	on $AsCl_3$	on the double salt
92—93[1]	—	—	—	—	—	—	—	—	—	—	—	—	19	38
92—93	—	—	—	—	—	—	—	—	—	—	—	—	15	20
92—93	—	—	—	—	$(C_6H_5)_2AsO$	9.5	14	189[2]	—	—	—	—	12.5	17
58—60	—	—	—	—	$(C_6H_5)_2AsCl_3$	4.5	6	192—196	—	—	—	—	33.5	49
—	—	—	—	—	$(C_6H_5)_2AsO$	23	17.5	189	—	—	—	—	23	17.5
92—94	—	—	—	—		7	10.5	189	—	—	—	—	27	30.5
91—93	—	—	—	—	$(C_6H_5)_2As(OH)_2$	16	24	189	63.54	63.24, 63.03	5.08	5.02, 5.06	28	36
								• • • • •						
87—90	—	—	—	—	—	—	—	—	—	—	—	—	34	43.5
91—92	—	—	—	—	—	—	—	—	—	—	—	—	17.5	22
154	47.08	47.10, 47.09	2.64	2.87, 2.84	—	—	—	—	—	—	—	—	40.5	48.5
153	—	—	—	—	$(ClC_6H_4)_2AsO$ ****	12.5	14	203	50.78	51.61, 51.46	2.84	3.05, 3.06	21.5	20
147	72.40	72.35, 72.45.	6.00	6.28, 6.09.	$(CH_3C_6H_4)_2AsO(OH)$	12.5	12.5	160	57.93	57.32, 57.51	5.21	5.58, 5.46	50	59.5
—	—	—	—	—	$(BrC_6H_4)_2As(OH)_2$****	4	5.5	76	37.45	37.27, 37.37	2.45	2.32, 2.33	36	40.5
					$(BrC_6H_4)_2AsO$	19	28.5	204—205	38.69	38.53, 38.66	2.17	2.38, 2.34		
171—173	20.28	19.76, 19.96	0.58	0.76, 0.73	—	—	—	—	—	—	—	—	33	66
169—171	—	—	—	—	$(Br_3C_6H_2)_3As$ ****	27	40	81—83	21.11	21.04, 21.02	0.59	0.65, 0.78	38	51

The arylation of arsenic trichloride by means of diazonium in complex form was studied in detail for the example of the double salts of phenyldiazonium chloride with ferric chloride and zinc chloride. As Table 1 shows, the ratio between the amounts of arylating and arylated reagents has a significant effect on the nature of the products. In general, an increase in the relative amount of the double salt is accompanied by an increase in the yield of triarylarsenic and triaryldichloroarsine, with a corresponding decrease in the yields of mono- and disubstituted trivalent arsenic derivatives. Thus, by variation of the reagent ratio it is possible to direct the reaction to preferential formation of mono-, di-, or trisubstituted products.

The formation of quinquevalent arsenic derivatives, namely Ar_3AsX_2, apparently occurs as the result of a secondary reaction of the double salt with the previously formed diphenylchloroarsine according to the equation:

$$Ar_2AsCl + ArN_2Cl \cdot MeCl_n \longrightarrow Ar_3AsCl_2 + N_2 + MeCl_n.$$

It is possible that the triarylarsenic isolated in some of the experiments was formed not directly, but as the result of reduction of triaryldichloroarsine by the metal present in excess. Thus, when zinc, a more powerful reducing agent than iron, is used for decomposition, quinquevalent arsenic derivatives are not formed at all. On the other hand, if excess double salt is added to the reaction mixture (obtained by decomposition of the double diazonium salt by means of the powdered metal followed by removal of excess) in absence of metal reducing agent, only $Ar_3A_2X_2$ is formed, without any Ar_3As. Apparently under these conditions the double diazonium salt decomposes by the action of ferrous chloride,

$$Ar_2AsCl + ArN_2Cl \cdot FeCl_3 \xrightarrow{FeCl_2} Ar_3AsCl_2,$$

since Ar_2AsCl and $ArN_2Cl \cdot FeCl_3$ do not react under normal conditions.

Two possible routes for the formation of arsenoorganic compounds in the reactions studied can be considered. On the one hand, it might be assumed that the metalorganic compound is formed as the result of a reaction between $AsCl_3$ and the aromatic radicals formed by the decomposition of the double diazonium salt by the metal powder, for example:

$$(1)\qquad \begin{cases} 2ArN_2Cl \cdot FeCl_3 + Fe \longrightarrow 2Ar\cdot + 2N_2 + 2FeCl_3 + FeCl_2 \\ Ar\cdot + AsCl_3 \longrightarrow [ArAsCl_3]\cdot \longrightarrow ArAsCl_2 + \cdot Cl \end{cases}$$

$$Fe + 2Cl\cdot \longrightarrow FeCl_2$$

On the other hand, it might be assumed that the metalorganic compound is formed only (or, at least, preferentially) as the result of the decomposition, by the powdered metal, of the double salt $ArN_2Cl \cdot AsCl_3$, formed from the double diazonium salt of ferric chloride (or zinc chloride) and $AsCl_3$, for example:

$$(2)\qquad \begin{cases} (a).\ ArN_2Cl \cdot FeCl_3 + AsCl_3 \rightleftharpoons ArN_2Cl \cdot AsCl_3 + FeCl_3, \\ (b)\ ArN_2Cl \cdot AsCl_3 + Fe \longrightarrow ArAsCl_2 + N_2 + FeCl_2, \\ (a')\ (ArN_2Cl)_2 \cdot ZnCl_2 + 2AsCl_3 \rightleftharpoons 2ArN_2Cl \cdot AsCl_3 + ZnCl_2, \\ (b')\ ArN_2Cl \cdot AsCl_3 + Fe \longrightarrow ArAsCl_2 + N_2 + FeCl_2. \end{cases}$$

It is seen that if the reaction takes this course, the stages (a) and (a') are reversible. If the reaction is carried out in the presence of excess $FeCl_3$ or $ZnCl_2$, the yields of arsenoorganic compounds shoud be decreased, as the equilibrium in (a) and (a') will be shifted to the left.

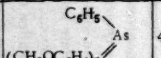
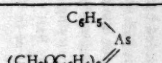
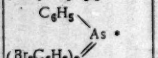
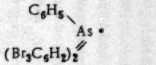
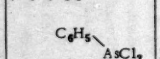
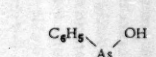
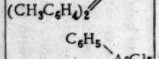
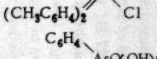
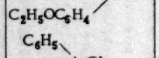
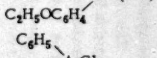
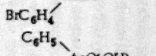
Experimental verification showed that when the reaction was carried out in the presence of excess $FeCl_3$ or $ZnCl_2$, the yield of the metalorganic compounds fell sharply (see Experiment Section, Experiment 5-8). In these cases the reactions proceeded much more slowly than usual; this indicates that the double salts $ArN_2Cl \cdot AsCl_3$ are decomposed much more easily by powdered metals than the double salts $ArN_2Cl \cdot FeCl_3$ and $(ArN_2Cl)_2 \cdot ZnCl_2$.

The same state of affairs apparently exists in the arylation of $ArAsCl_2$. For example, the double salt $(p\text{-}CH_3OC_6H_4N_2Cl)_2 \cdot ZnCl_2$ is not decomposed in acetone by powdered iron in the cold. However, decomposition commences immediately on addition of phenyldichloroarsine*. The latter apparently forms a double diazonium salt, which is readily decomposed by iron:

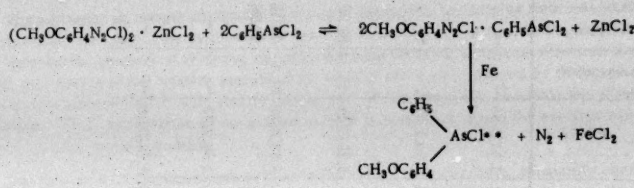
* In absence of powdered metal, phenyldichloroarsine does not decompose $(CH_3OC_6H_4N_2Cl)_2 \cdot ZnCl_2$.

TABLE 2

Substances Formed by Arylation of Phenyldichloroarsine by Double Salts of Zinc Chloride (decomposition by means of iron in acetone)

Experiment No.	Double salt	Moles of double salt to moles of $C_6H_5AsCl_2$	g-Atoms of Fe to moles of double salt	Arsenoorganic compounds of the type $ArAr'_2As$, $ArAr'_2AsX_2$, $ArAr'AsX$: Formula	Yield (%) on $C_6H_5AsCl_2$	Yield (%) on the double salt	Identified as the compound	Melting point	analysis (%) C Calculated	C Found	H Calculated	H Found	As Calculated	As Found
1	$(p\text{-}CH_3OC_6H_4N_2Cl)_2 \cdot ZnCl_2$	1/1	2/1		40	40		76–79°	65.56	65.63, 65.82	5.22	5.50, 5.55	–	–
2	$(2,4,6\text{-}Br_3C_6H_2N_2Cl)_2 \cdot ZnCl_2$	1/1	2/1		30	30		185	27.72	27.95, 27.80	1.16	1.30, 1.22	–	–
3	$(p\text{-}CH_3C_6H_4N_2Cl)_2 \cdot ZnCl_2$	1/2	4/1		17	34		154–156	62.12	62.35, 62.28	5.21	5.35, 5.41	19.37	19.05
4	$(p\text{-}C_2H_5OC_6H_4N_2Cl)_2 \cdot ZnCl_2$	1/1	2/1		30	15		158	54.95	55.47, 55.28	4.94	5.36, 5.32	24.47	24.16, 24.23
5	$(p\text{-}BrC_6H_4N_2Cl)_2 \cdot ZnCl_2$	1/1	2/1		72	36		b.p 215–222° (5mm)	41.96	42.59, 42.42	2.64	2.88, 2.83	–	–
								178–180	42.26	42.19, 42.37	2.95	3.23, 3.35	–	–

* substance described for the first time.



The method developed for the synthesis of aromatic arsenoorganic compounds is of undoubted preparative interest. The total yields, which vary in the range 30-70%, could undoubtedly be increased in several instances by the use of larger quantities. The method has a number of advantages over Bart's diazo method which is the most widely used method at present for the synthesis of aromatic arsenoorganic compounds. Thus, the double salt method makes it possible to prepare any of three types of trivalent arsenoorganic compounds ($ArAsX_2$, Ar_2AsX, Ar_3As). The aryldichloroarsines are obtained direct by this method, and not through the corresponding acids; the synthesis of simple and mixed diarylchloroarsines is effected in one and two stages respectively, while Bart's method requires four stages for the preparation of both types of compounds (arylarsinic acid → arylarsine oxide → diarylarsinic acid → diarylchloroarsine) with very low final yields. The method used by Takahashi [4] for the synthesis of mixed diaryl arsenic derivatives by the arylation of aryldichloroarsines by means of the corresponding free diazonium compounds is inconvenient as a preparative method because of the explosive character of the diazonium compounds. Mixed triarylarsines up to the present time have only been synthesized with the aid of other metalorganic compounds. Only very few representatives of this class are known. The double diazonium salt method makes these compounds quite accessible.

An example of a preparative application of this method is provided by the synthesis of phenyldichloroarsine with the aid of vacuum distillation. The yield of phenyldichloroarsine is 29% (calculated on the double salt and on $AsCl_3$ •) the yield of diphenylchloroarsine is 17% (on $AsCl_3$) and 35% (on the double salt). In the synthesis of phenyldichloroarsine from arsenic trioxide via phenylarsinic acid prepared by Bart's method, the yield of phenyldichloroarsine is 25-27% (calculated on As_2O_3). The time required for carrying out the synthesis by the double salt method is 6-7 hours (including the preparation of the double salt), and by Bart's method it is 13-14 hours. The volume of the reaction vessel used in Bart's method is 5-6 times as great as in the double salt method.

EXPERIMENTAL

1. Reaction of the double salt of phenyldiazonium chloride and ferric chloride with arsenic trichloride. (Experiment 1, Table 1). 13.5 g (0.044 mole) of the double salt of phenyldiazonium chloride and ferric chloride was added in 30 minutes with stirring to a solution of 8 g (0.044 mole) of arsenic trichloride in 50 ml of dry acetone, to which 14 g (0.25 g-atom) of iron powder had been added. The reaction vessel was cooled with ice-cold water. When evolution of gas stopped, the reaction mass was filtered to remove unreacted iron. The acetone was evaporated from the filtrate, and the residue (a dark viscous liquid) was washed with HCl (1:1), water, and hydrolyzed with 40 ml of KOH (1:1). The mixture became thick. After 1 hr. precipitate was filtered off; traces of phenylarsine oxide were detected in the filtrate (by addition of saturated aqueous ammonium chloride solution). The residue was washed with water, dried, and extracted with acetone. After evaporation of the acetone the precipitate crystallized. M.p. 92-93° (after recrystallization from ligroine). The literature gives m.p. 91-92° for diphenylarsine oxide [5]. Experiments 2-4, 6, and 7 (Table 1) were carried out analogously.

2. Reaction of the double salt of phenyldiazonium chloride and zinc chloride with arsenic trichloride. 45 g (0.11 mole) of the double salt of phenyldiazonium chloride and zinc chloride was suspended in 130 ml of dry acetone in which 40 g (0.22 mole) of arsenic trichloride was dissolved. The mixture was cooled to −5°, and 12.3 g (0.22 g-atom) of iron powder was added in 1.5 hours with vigorous stirring. When gas evolution ceased the reaction mass was filtered to remove the inorganic precipitate, the precipitate was washed with acetone, and the solvent was removed from the combined filtrates at the water jet pump at 30-40°. The residue was thoroughly washed with HCl (1:1) and then with dilute HCl; the organic layer was extracted with chloroform and dried with fused $CaCl_2$, the solvent was distilled off, and the residue (a mixture of phenyldichloroarsine and diphenylchloroarsine) was distilled under vacuum. The following fractions were collected: 1st, 120-160° (12 mm), phenyldichloroarsine with an admixture of diphenylchloroarsine; 2nd, 160-200° (12 mm), pure diphenylchloroarsine. A second distillation of

• As $AsCl_3$ is obtained almost quantitatively from As_2O_3, for practical purposes this yield applies also to As_2O_3.

•• Phenyl-di-p-methoxyphenylarsine was formed as the final reaction product.

each of the fractions yielded 14 g (29%) of phenyldichloroarsine, b.p. 125-130° (12 mm)* and 10 g of diphenylchloroarsine (17% calculated on $AsCl_3$, 35% calculated on the double salt), b.p. 170-180° (12 mm)**. The total yield of arsenoorganic compounds was 46% (calculated on $AsCl_3$), 64% (on the double salt). Experiments 8-10, 12-14 were carried out similarly (Table 1).

3. Reaction of the double salt of 2,4,6-tribromophenyldiazonium chloride and zinc chloride with arsenic trichloride. (Experiment 14, Table 1). 38 g (0.068 g-atom) of powdered iron was added during 1 hour with stirring to a suspension of 15 g (0.017 mole) of the double salt in 70 ml of dry acetone, in which 6.1 g (0.034 mole) of arsenic trichloride had been dissolved. The mixture was cooled to −5°. The precipitate of double salt gradually dissolved. At the end of the addition of iron a precipitate was formed. The reaction mass was heated till the precipitate dissolved (~60°) and filtered while hot to remove the inorganic precipitate. The filtrate was evaporated; the solid residue was thoroughly washed with a considerable amount of HCl (1:1), filtered off, and treated with water. The weight after drying was 7.8 g (66% on the double salt). After a single recrystallization from alcohol and then from dichloroethane, m.p. was 171-173°. The substance is white in color, and is moderately soluble in acetone, alcohol, and dichloroethane, and with difficulty in ether. Experiments 8-10, 12, 13 (Table 1) were carried out similarly.

4. Reaction of the double salt of 2,4,6-tribromophenyldiazonium chloride and zinc chloride with arsenic trichloride, followed by addition of excess double salt to the reaction mixture. (Experiment 15, Table 1). The reaction between 5 g (0.006 mole) of the double salt of 2,4,6-tribromophenyldiazonium chloride and zinc chloride, 2.2 g (0.012 mole) of arsenic trichloride, and 1.3 g (0.024 g-atom) of iron powder was carried out in the conditions of the preceding experiment. The volume of the solvent (acetone) was 30 ml. When gas evolution ceased and the inorganic precipitate had been filtered off, the filtrate was cooled to 0°, and a further 5 g (0.006 mole) of the double salt was added in 0.5 hour; the salt decomposed more slowly than in the presence of iron. The precipitate which formed was filtered off and washed with acetone; the wash acetone was added to the filtrate. The weight of the precipitate was 0.9 g, m.p. 169-171° (from dichloroethane). A mixed sample with known di-2,4,6-tribromophenylarsine oxide showed no melting point depression. Yield 11%. The filtrate was evaporated. The solid residue after recrystallization from methyl alcohol melted at 81-83°. Yield 3.3 g (40% calculated on the double salt). The substance has a cream color, and is easily soluble in dichloroethane, moderately in acetone, and badly in ether. Experiments 5 and 11 (Table 1) were carried out similarly.

5. Reaction of the double salt of phenyldiazonium chloride and ferric chloride with arsenic trichloride in presence of ferric chloride. 25 g of iron powder (0.044 g-atom) was added in 1 hour with stirring to a suspension of 6.7 g of the double salt of phenyldiazonium chloride and ferric chloride (0.022 mole) in 50 ml of acetone, in which 4 g of arsenic trichloride (0.022 mole) and 12 g of anhydrous ferric chloride (0.075 mole) had been dissolved. The reaction started at +10°, gas evolution was slow and ended only after several hours. The mixture was filtered to remove the inorganic precipitate, the precipitate was washed with acetone, the acetone was evaporated off from the combined filtrates, and the residue was thoroughly washed with HCl (1:1). It was not possible to isolate individual arsenoorganic compounds from the organic layer by means of the usual treatment.

6. Reaction of the double salt of phenyldiazonium chloride and zinc chloride with arsenic trichloride, with addition of zinc chloride to the reaction mixture. 5 g of iron powder (0.09 g-atom) was added in 1 hour to a vigorously stirred suspension of 11.5 g of the double salt (0.025 mole) in 40 ml of acetone, in which 4.5 g (0.025 mole) of arsenic trichloride and 33 g (0.24 mole) of anhydrous zinc chloride had been dissolved. The reaction vessel was fitted with a calcium chloride tube. The reaction mixture was cooled to −5°. Evolution of gas (very slow) only started 20 minutes after the start of the addition of iron powder. The cooling was stopped at the end of the addition. Gas evolution continued several more hours. The reaction mass was filtered to remove the inorganic precipitate which was washed with acetone, and the acetone was driven off from the combined filtrates; the residue was washed with HCl (1:1) and the organic layer was separated off and hydrolyzed by means of KOH. The precipitate (viscous resinous mass) was separated off, washed with water, dried and extracted with acetone. After evaporation of the acetone, a very resinous mass was left, which did not crystallize even when left 1 month, and from which individual arsenoorganic compounds could not be isolated.

7. Reaction of the double salt of phenyldiazonium chloride and zinc chloride with arsenic trichloride in the conditions of the preceding experiment, but without addition of zinc chloride. The amounts of reagents and solvent were the same as in the preceding experiment, and the reaction was carried out in the same conditions. Nitrogen evolution started immediately after the start of the addition of iron, proceeded vigorously, and ceased after 40 minutes.

* Literature data: b.p. 250-255° (760 mm) [6].

** Literature data: b.p. 333° (760 mm) [7].

The reaction mixture was treated as in the preceding experiment. After evaporation of the solvent from an acetone extract of the hydrolyzed mass, a viscous liquid remained, which soon crystallized. Part of the substance dissolved when treated with a small amount of ether; after evaporation of the ether, triphenylarsenic remained and gradually crystallized. M.p. 57° (from methyl alcohol) *. Yield 1.4 g (18.5% calculated on $AsCl_3$, 25% on the double salt).

The portion insoluble in ether was triphenylarsine oxide. M.p. 187° (from benzene)** Yield 0.9 g (11% calculated on $AsCl_3$, 15% on the double salt). The total yield of arsenoorganic compounds was 29.5% (calculated on $AsCl_3$), and 40% (on the double salt).

8a. Reaction of the double salt of p-tolyldiazonium chloride and zinc chloride with arsenic trichloride in presence of zinc chloride. 6.3 g (0.112 g-atom) of iron powder was added in 1 hour with stirring to a suspension of 24.7 g (0.056 mole) of the double salt in 70 ml of acetone, cooled to 0°, in which 10 g (0.056 mole) of arsenic trichloride and 38 g (0.28 mole) of anhydrous zinc chloride had been dissolved. The decomposition proceeded slowly and was completed only after several hours (the cooling was stopped at the end of the addition of iron). The mixture was filtered to remove the inorganic precipitate, which was washed with acetone, and the acetone was removed from the combined filtrates by evaporation. The remaining resinous mass was thoroughly washed with HCl (1:1) (shaken mechanically for 2 hours) and with water; the organic layer (18.4 g) was separated off and hydrolyzed by KOH (40%); the viscous mass of the hydrolysis products was filtred off, washed with water, dried, and extracted with acetone. The acetone solution was evaporated. A very resinous noncrystallizing mass remained.

8b. Reaction of the double salt of p-tolyldiazonium chloride and zinc chloride with arsenic trichloride without excess of zinc chloride ***. The amounts of reagents, solvent, and the reaction conditions were the same as in the preceding experiment. Zinc chloride was not added to the reaction mixture. The decomposition proceeded vigorously and was complete in 45 minutes. The treatment of the reaction mixture was the same as in the preceding experiment. The weight of the liquid mixture of reaction products after washing with HCl and water was 19.8 g. After evaporation of the solvent from an acetone extract of the hydrolyzed mass, a transparent yellow viscous mass remained, which crystallized after several hours.

The parallel experiments (8a and 8b) were repeated in the same conditions (Experiment 8c, with addition of $ZnCl_2$, 8d without addition of $ZnCl_2$). The weight of the liquid mixture of reaction products after washing with HCl and water was 18 g in Experiment 8c, and 19.5 g in Experiment 8d. In all these experiments the total percentage of organically combined arsenic was determined in the mixture which remained after evaporation of the solvent from an acetone extract of the hydrolyzed and dried mass. In all the experiments (a,b,c,d) it was established that no arsenoorganic compounds were present in the alkaline filtrate obtained after hydrolysis, and it was also shown that the extraction of the hydrolysis products by acetone was complete.

Determination of the percentage arsenic content in the reaction products (in Experiments 8a, 8b, 8c, 8d). Arsenic was determined gravimetrically, by oxidation of a weighed sample by means of fuming nitric acid, precipitation as magnesium pyroarsenate (by Morgan and Walton's method [8]), solution of the precipitate in HCl, precipitation by hydrogen sulfide, and weighing as the pentasulfide.

Analytical results:

Experiment 8a (with addition of $ZnCl_2$). Found %: As 7.5.

Experiment 8b (without addition of $ZnCl_2$). Found %: As 14.1.

Experiment 8c (with addidtion of $ZnCl_2$). Found %: As 9.16.

Experiment 8d (without addition of $ZnCl_2$). Found %: As 16.73.

9. Reaction of the double salt of p-bromophenyldiazonium chloride and zinc chloride with phenyldichloroarsine. (Experiment 5, Table 2). 5 g (0.09 g-atom) of iron powder was added in 1 hour with vigorous stirring to a suspension of 25.8 g (0.04 mole) of the double salt of p-bromophenyldiazonium chloride and zinc chloride, cooled to 0°, in which 10 g (0.045 mole) of phenyldichloroarsine had been dissolved. When the addition of iron and gas evolution ceased (after standing 15 minutes with the cooling stopped), the reaction mass was filtered to remove the

* Literature data: m.p. 58-60.5° [7].

** Literature data: m.p. 189° [7].

*** Parallel to the preceding experiment.

inorganic precipitate, which was washed with acetone, and the solvent was removed from the combined filtrates under reduced pressure (water jet pump) at 40-50°. The remaining thick liquid was thoroughly washed with HCl (1:1). The organic layer was extracted with chloroform. The chloroform extract was dried with fused Na_2SO_4, the solvent was distilled off, and the residue distilled under vacuum. The fraction boiling at 200-225° (5 mm) was collected. Yield 12 g. Part of the substance was oxidized by the action of aqueous (30%) hydrogen peroxide solution. The resultant phenyl-p-bromophenylarsinic acid melted at 178-180° after recrystallization from water and a single precipitation from chloroform by means of ether. Literature data: m.p. 184-185° [9].

The remaining phenyl-p-bromophenylchloroarsine was redistilled twice: b.p. 215-222° (5 mm). Literature data: b.p. 184-186° (0.3 mm) [10]. Experiments 1-4 (Table 2) were carried out similarly.

SUMMARY

1. The decomposition of double diazonium salts of ferric chloride and zinc chloride by means of powdered metals in the presence of arsenic trichloride and aryldichloroarsines was studied.

2. Conditions were developed in which this reaction can serve as a convenient method for the synthesis of arsenoorganic compounds, including compounds with mixed radicals.

3. The mechanism of these reactions has been studied.

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THE DIRECT SYNTHESIS OF PROPYL-, ISOPROPYL-, BUTYL-, AND ISOBUTYLSILANES

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The direct synthesis of alkylchlorosilanes prepared from methyl chloride and ethyl chloride has been relatively well studied [1]. The literature contains data on the effects of temperature on the yields of various alkylchlorosilanes [2]. For example, it is reported that, for methyl chloride in the temperature range 280-400°, the yields vary within the following limits: $(CH_3)_2SiCl_2$ 35-80%, CH_3SiCl_3 10-40%, $SiCl_4$ + $HSiCl_3$ + $(CH_3)_3SiCl$ + CH_3HSiCl_2 5-25%.

The following yields are reported for 300° [1,3]: $(CH_3)_2SiCl_2$ 42.1%, CH_3SiCl_3 36.8%, CH_3HSiCl_2 11.8%, $SiCl_4$ + $HSiCl_3$ + $(CH_3)_3SiCl$ 9.4%.

For ethyl chloride and at 300-325° the following yields are given [1,4]: $(C_2H_5)_2SiCl_2$ 26%, $C_2H_5SiCl_3$ 27%, $(C_2H_5)_3SiCl$ + $SiCl_4$ + $C_2H_5HSiCl_2$ 47%.

This shows that dialkyldichlorosilanes and monoalkyltrichlorosilanes predominate in the mixtures of alkylchlorosilanes, while the yields of alkyldichlorosilanes are not high. As regards the direct synthesis based on higher saturated alkyl halides, there are some very dubious data [5] according to which no isopropylchlorosilanes were found when isopropyl chloride was used for the synthesis. Mamedaliev and Musrafaev [6] isolated isopropyltrichlorosilane and diisopropyldichlorosilane from the alkylchlorosilanes obtained from iso-C_3H_7Cl, and tert-butyltrichlorosilane from the alkylchlorosilanes obtained from tert-C_4H_9Cl, but they reported neither the data on the distillation of the alkylchlorosilanes, nor the yields of the individual products from the synthesis.

The results of our study showed that as the length of the hydrocarbon radical in the original alkyl chloride increases, there is a sharp decrease in the yield of dialkyldichlorosilanes and a sharp rise in the yield of alkyldichlorosilanes, caused by removal of hydrogen chloride from the alkyl chloride. The alkylchlorosilanes obtained are listed in Table 1, and the distillation curves are shown in Figures 1 and 2. The alkylchlorosilanes were converted into diallylalkylsilanes by the action of $CH_2=CH-CH_2MgX$ (Table 2).

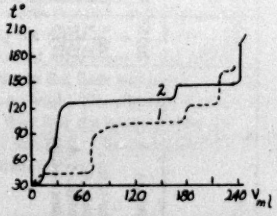

Fig. 1. Distillation curves
1) Propylchlorosilanes, 2) butylchlorosilanes.

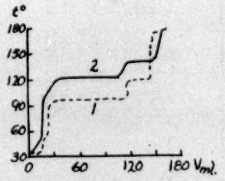

Fig. 2. Distillation curves
1) Isopropylchlorosilanes, 2) isobutychlorosilanes.

EXPERIMENTAL

Propylchlorosilanes. A glass tube (600 mm long, 44 mm diameter) filled with pieces (5-10 mm) of an alloy of Si (80%) and Cu (20%) was placed in a tubular electric furnace. The total weight of alloy was 500 g. Propyl chloride was passed through the tube at a rate of 20 g/hour at 350 ± 10°. The reaction products were condensed by a water condenser. 493 g (554 ml) of propyl chloride yielded 312 g (294 ml) of condensate. Distillation of the reaction mixture on a column 1100 mm high filled with glass rings 3 mm diameter yielded the following fractions (distillation curve is shown in Fig. 1): 1st, b.p. up to 67.5°, 74.6 g (24%), containing 53 g (17%) of unreacted pro-

TABLE 1

Serial No.	Compounds	B.p.	P in (mm)	d_4^{20}	n_D^{20}	MR_D found	MR_D calc.	Elementary analysis (%) C found	C calculated	H found	H calculated	Si found	Si calculated	Cl found	Cl calculated
1	$C_2H_5SiHCl_2$	99°	740	1.0546	1.4216	34.47	34.43	25.18	26.70, 26.51	5.64	5.85, 5.83	19.63	18.81, 18.80	49.55	48.59, 48.72
2	$C_2H_5SiCl_3$	122.2	740	1.1851	1.4290	38.62	38.43	—	—	—	—	—	—	—	—
3	$(C_2H_5)_2SiCl_2$	171.5	753.5	1.0174	1.4411	48.07	48.06	—	—	—	—	—	—	—	—
4	$C_4H_9SiHCl_2$	126.5	742	1.0426	1.4310	39.01	39.06	—	—	—	—	—	—	—	—
5	$C_4H_9SiCl_3$	146.5	741	1.1603	1.4379	43.33	43.06	25.07	25.75, 25.81	4.73	4.77, 4.76	55.52	54.01, 54.02	14.66	15.08, 14.94
6	$iso\text{-}C_3H_7SiHCl_2$	95.3	744.5	1.0573	1.4222	34.41	34.43	25.18	25.76, 25.87	5.64	5.68, 5.56	19.63	19.33, 19.63	49.55	48.48, 48.92
7	$iso\text{-}C_3H_7SiCl_3$	120.3	747.8	1.1934	1.4319	38.58	38.43	—	—	—	—	—	—	—	—
8	$iso\text{-}C_4H_9SiHCl_2$	120.5	746	1.0295	1.4270	39.18	39.06	30.57	30.93, 31.06	6.87	6.65, 6.57	17.87	16.98, 16.87	45.13	45.06, 45.47
9	$iso\text{-}C_4H_9SiCl_3$	139.5	744.7	1.1467	1.4358	43.66	43.06	—	—	—	—	—	—	—	—

TABLE 2

Serial No.	Compounds	B.p.	P in (mm)	d_4^{20}	n_D^{20}	MR_D found	MR_D calc.	Elementary analysis (%) C found	C calculated	H found	H calculated	Si found	Si calculated	Yield(%)
1	$(CH_2{=}C(CH_3){-}CH_2)_2SiH(C_6H_7)$	200.5°	741	0.8037	1.4611	62.318	62.01	72.44	72.12, 72.35	12.16	11.97, 11.78	15.40	15.95, 15.66	58.0
2	$(CH_2{=}CH{-}CH_2)_2SiH(C_6H_7)$	165.8	740	0.7833	1.4526	53.19	53.11	70.04	69.95	11.75	11.69	18.2	17.9	29.0
3	$(CH_2{=}CH{-}CH_2)_2SiH(C_4H_9)$	187.3	745.8	0.7944	1.4579	57.80	57.74	71.34	71.55, 71.36	11.97	11.95, 11.90	16.68	16.25, 16.60	39.0
4	$(CH_2{=}CH{-}CH_2)_2SiH(iso\text{-}C_4H_9)$	157.2	743.3	0.7853	1.4539	53.20	53.11	70.04	70.13	11.75	11.60	18.20	18.29	30.5
5	$(CH_2{=}CH{-}CH_2)_2SiH(iso\text{-}C_4H_9)$	179.3	727.4	0.7900	1.4556	57.86	57.74	71.34	71.32, 71.36	11.97	11.81, 11.80	16.68	16.19, 16.54	55.5

pyl chloride; 2nd, b.p. 67.5-95°, 12.4 g (4%); 3rd, b.p. 95-103°, 86.4 g (27.7%) (propyldichlorosilane); 4th, b.p. 103-120°, 11 g (3.5%); 5th, b.p. 120-124°, 49 g (15.6%) (propyltrichlorosilane); 6th, b.p. 124-167°, 21 g (6.2%).

In a second experiment at 280-290°, 473 g of propyl chloride yielded 289 g of condensate, which contained: 94 g of propyldichlorosilane (32.5%), 55 g of propyltrichlorosilane (19%), and 28.5 g of dipropyldichlorosilane (10%).

All the other experiments were carried out under the same conditions (described above) but at 350°.

Butylchlorosilanes. 770 g of butyl chloride, passed through the furnace at 20.7 g/hour, yielded 440 g of condensate, from the distillation of which the following fractions were obtained: 1st, b.p. up to 120°, 41.2 g (9.4%); 2nd, b.p. 120-131°, 134 g (30.5%) (butyldichlorosilane); 3rd, b.p. 131-143°, 6.6 g (1.5%); 4th, b.p. 143-149°, 80.3 g (18.2%) (butyltrichlorosilane); 5th, b.p. 149-205.5°, 8.3 g (1.9%); residue 11.4 g (2.6%).

To determine the quantity of butenes formed by the removal of HCl from butyl chloride, a trap cooled by a mixture of dry ice and acetone was fitted after the receiver for the condensate. 264 g of butyl chloride yielded 170 g of crude mixture condensed in the water condenser, and 99 ml in the trap. Bromine was added to the latter at −50° till a crimson color appeared. The mixture of bromides formed was treated with water to remove bromosilanes, and the residue was distilled under vacuum. 94.2 g of dibromobutanes was obtained, with b.p. 46-47° at 15 mm, d_4^{20} 1.7896, n_D^{20} 1.5129, which corresponds to 30.4 g of decomposed butyl chloride, or 115% of the amount passed through the furnace.

Isopropylchlorosilanes. 384 g of isopropyl chloride passed through the furnace at 18 g/hour yielded 110 g of condensate; a large amount of gaseous products was also formed, and soot and tar formed in the tube. The condensate yield fell as the isopropyl chloride was passed through the tube. The following fractions were obtained in distillation: 1st, b.p. 31-89°, 8.8 g (8%). 2nd, b.p. 89-95.3°, 41.8 g (38.2%) (isopropyldichlorosilane); 3rd, b.p. 95.3-115°, 6.6 g (6%); 4th, b.p. 115-120.6°, 24 g (21.3%) (isopropyltrichlorosilane); 5th, b.p. 120.6-168°, 4.2 g (3.8%); 6th, b. p. 168-170°, 12 g (11%) (apparently diisopropylidichlorosilane); residue 7 g (6.4%).

At 300°, 564 g of isopropyl chloride yielded 227.5 g of condensate, which contained: 96 g (42.3%) of isopropyldichlorosilane, and 29 g (12.9%) of isopropyltrichlorosilane. As in the case of butyl chloride, isopropyl chloride decomposed to form propylene, which was identified as 1,2-dibromopropane; b.p. 21.2° at 15 mm, d_4^{20} 1.9314, n_D^{20} 1.5195.

Isobutylchlorosilanes. 413 g of isobutyl chloride passed through the furnace at 18 g/hour yielded 269 g of condensate. The following fractions were obtained: 1st, b.p. up to 115.5°, 32.8 g (12.2%); 2nd, b.p. 115.5-118.2°, 2.3 g (0.8%); 3rd, b.p. 118.2-124°, 78.8 g (29.3%) (isobutyldichlorosilane); 4th, b.p. 124-138°, 8.6 g (3.2%); 5th, b.p. 138-140°, 39 g (14.5%) (isobutyltrichlorosilane); 6th, b.p. 140-170°, 23 g (8.5%); residue 14.5 g (5.4%).

Diallylalkylsilanes. All the diallylalkylsilanes and dimetallylpropylsilane (Table 2) were prepared by the Grignard-Wurtz reaction, under approximately the same conditions. As an example of a typical synthesis, we describe only the preparation of diallylpropylsilane. A mixture of 28.6 g (0.2 mole) of propyldichlorosilane and 72.6 g (0.6 mole) of allyl bromide was added during 6 hours to 19.5 g (0.8 mole) of Mg in 400 ml of ether. At the end of the addition the flask was heated 5 hours on the water bath, and the contents were then treated with water and hydrochloric acid. The ether layer, and ether extracts from the aqueous layer, were dried over $CaCl_2$. After removal of the ether the heavy residue was distilled over a column with 25 theoretical plates. 9 g of propyldiallylsilane was obtained. The molecular refractions were calculated as described previously [7], with a correction [8] for allylsilanes.

SUMMARY

1. The direct synthesis of alkylchlorosilanes from n-C_3H_7Cl, iso-C_3H_7Cl, n-C_4H_9Cl, and iso-C_4H_9Cl has been studied. It was established that these alkyl chlorides give higher yields of alkyldichlorosilanes ($RHSiCl_2$) and much lower yields of dialkyldichlorosilanes (R_2SiCl_2) than ethyl chloride and especially than methyl chloride.

2. Four diallylalkylsilanes and dimetallylpropylsilane were synthesized by the reactions of allylmagnesium bromide and metallylmagnesium chloride with alkyldichlorosilanes.

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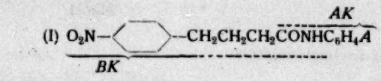
ISOLATED CHROMOPHORE SYSTEMS

XXX. COLOR PHENOMENA IN ARYLAMIDES OF γ-(2,4-DINITROPHENYL)BUTYRIC ACID

E. A. Smirnov

It was shown in one of our earlier communications [1] that arylamides of γ-(4-nitrophenyl)butyric acid with the general Formula (I) may have



(I) O_2N—(BK)—$CH_2CH_2CH_2CONHC_6H_4A$ (AK)

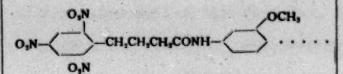
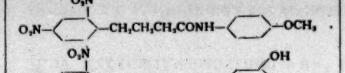
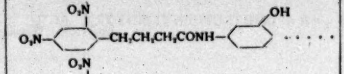
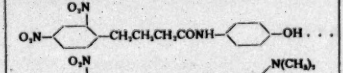
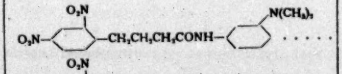
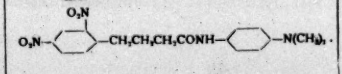
A = p-OCH_3, p-OH, p-$N(CH_3)_2$, m-OCH_3, m-OH, m-$N(CH_3)_2$

visible color despite the fact that the link between the benzene nuclei in these compounds contains three CH_2 groups, the presence of which excludes the possibility of formation of a continuous conjugated chain. This should serve as a further confirmation of our repeatedly expressed view [2] that the main cause of color in compounds of this type should be sought in direct interaction between electronophilic (BK) and electron-donor (AK) chromophore systems with formation of complex compounds.

By a comparison of the color of this series of compounds with the color of the corresponding derivatives of 4-nitrophenylacetic and 4-nitrohydrocinnamic acids it was possible to establish the laws governing the change of color in the transition from one series to another. Conclusions drawn on the basis of visual observations were further confirmed [3] by studies of the reflection and absorption spectra of these compounds.

In the present communication analogous derivatives, containing two nitro groups in the 2,4 positions, are examined. The introduction of a second NO_2 group should lead to intensification of the electronophilic properties of the nitroenoid chromophore system, and consequently also to an increase of its complex-forming power and to a deepening of the color of the compounds. As the data of Table 1 show, all the compounds synthesized were colored (in the mononitro derivatives the representatives with OCH_3 groups are colorless), and in the presence of the powerful electron-donor group $N(CH_3)_2$ the color becomes deep red, almost black (Table 1, No. 6). Table 2 shows a comparison of the colors of these compounds with those of the corresponding derivatives of 2,4-dinitrophenylacetic and 2,4-dinitrohydrocinnamic acids, described previously [4]. From this comparison we may conclude that compounds containing an electron-donor group in the meta position to the NH group generally obey the same law as the corresponding mononitro derivatives [5], namely: derivatives of 2,4-dinitrophenylbutyric acid, like the derivatives of 2,4-dinitrophenylacetic acid, are, as a rule, less deeply colored than the corresponding derivatives of 2,4-dinitrohydrocinnamic acid. This is seen particularly clearly in compounds containing a m-$N(CH_3)_2$ group, of which the 2,4-dinitrohydrocinnamic acid derivative is light red, the corresponding derivative of 2,4-dinitrophenylbutyric acid is only orange, while the 2,4-dinitrophenylacetic acid is brownish yellow (or orange-red). This is also seen fairly clearly in compounds containing a m-OH group: the pale yellow color of the 2,4-dinitrophenylbutyric acid derivative is less deep than the light yellow color of the corresponding compounds in the other two series. The two latter compounds in powder form are very similar in color, although in the crystalline form the dinitrohydrocinnamic acid derivative has clearly a rather deeper color. It is only in compounds with a m-OCH_3 group that the dinitrophenylbutyric acid derivative does not differ appreciably in color from the

TABLE 1

Serial No.	Formulas of compounds	Color of substance in crystal form	Color of substance in powder form
1		Greenish yellow	Pale yellow •
2		Pale greenish yellow	Pale yellow
3		Greenish yellow	Pale yellow
4		Orange-yellow	Yellow
5		Red-yellow	Orange
6		Very deep red (almost black)	Deep red

• The second form of this compound is almost colorless .

TABLE 2

Comparative Color (in Powder Form) of Arylamides of 2,4-Dinitrophenylacetic, 2,4-Dinitrohydrocinnamic, and γ-(2,4-Dinitrophenyl)butyric Acids of the General Type $RNHC_6H_4A$

Electron-donor group (A)	R = 2,4-$(O_2N)_2C_6H_3CH_2CO$	R = 2,4-$(O_2N)_2C_6H_3(CH_2)_2CO$	R = 2,4-$(O_2N)_2C_6H_3(CH_2)_3CO$
m-OCH_3	Almost colorless	Pale yellow	Pale yellow ••
p-OCH_3	Yellow	Light yellow	Pale yellowish
m-OH	Light yellow	Light yellow	Pale yellow
p-OH	Bright yellow	Light yellow	Yellow
m-$N(CH_3)_2$	Brownish-yellow •••	Light red	Orange
p-$N(CH_3)_2$	Brownish red	Orange-red	Dark red

•• The second form of this compound is almost colorless .

••• Another form of this compound is reddish-orange in color.

corresponding dinitrohydrocinnamic acid derivative. Thus, there is a color change sequence in the transition from one series of compounds to another; at first, in the transition from dinitrophenylacetic to dinitrohydrocinnamic acid derivatives there is some deepening of color, and later, in the transition from dinitrohydrocinnamic to dinitrophenylbutyric acid derivatives there is an increase of color (compounds with OCH_3 group are an exception).

For compounds containing an electron-donor group in the para position, the dinitrophenylbutyric acid derivatives, on the contrary, are as a rule more deeply colored than the dinitrohydrocinnamic derivatives (Table 2). This is seen very clearly in compounds with a p-$N(CH_3)_2$ group, which have a deep red color, while the corresponding derivative of dinitrohydrocinnamic acid is only orange-red; it is also seen quite clearly in compounds with a p-OH group, in which the dinitrophenylbutyric acid derivative is yellow, while the dinitrohydrocinnamic derivative is only light yellow. As the corresponding dinitrophenylacetic acid derivatives are also deeper in color than the dinitrohydrocinnamic acid derivatives, it follows that here also we have a color change sequence in the transition from phenylacetic to hydrocinnamic acid derivatives, but in the reverse order: the color is first increased, and then deepened. However, here also this rule is not followed by compounds with a OCH_3 group, and the dinitrophenylbutyric acid derivative is less deeply colored (pale yellowish) than the corresponding dinitrohydrocinnamic acid derivative (light yellow).

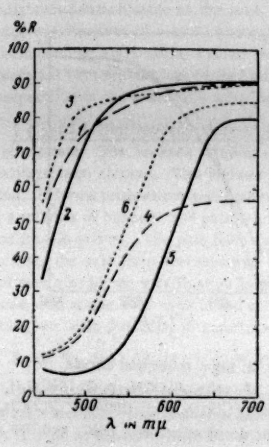


Fig. 1. Light reflection curves.
1) DPA-NHC_6H_4OH-m 2) DHC-NHC_6H_4OH-m, 3) DPB-NHC_6H_4OH-m, 4) DPA-$NHC_6H_4N(CH_3)_2$-m, 5) DHC-$NHC_6H_4N(CH_3)_2$-m, 6) DPB-$NHC_6H_4N(CH_3)_2$-m, [DPA) 2,4-$(O_2N)_2C_6H_3CH_2CO$, DHC) 2,4-$(O_2N)_2C_6H_3(CH_2)_2CO$, DPB) 2,4-$(O_2N)_2C_6H_3(CH_2)_3CO$].

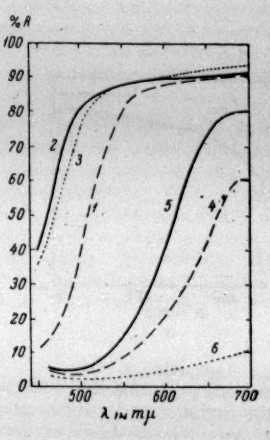


Fig. 2. Light reflection curves.
1) DPA-NHC_6H_4OH-p, 2) DHC-NHC_6H_4OH-p, 3) DPB-NHC_6H_4OH-p, 4) DPA-$NHC_6H_4N(CH_3)_2$-p, 5) DHC-$NHC_6H_4N(CH_3)_2$-p, 6) DPB-$NHC_6H_4N(CH_3)_2$-p. (The deisgnations DPA, DHC, and DPB are the same as in Fig. 1).

A comparison of color of dinitrophenylbutyric acid derivatives with the color of the corresponding dinitrophenylacetic acid derivatives shows that the former, as a rule, have a tendency to some increase of color in comparison with the latter (similar behavior is also found in the corresponding mononitro derivatives). An exception is provided by compounds containing m-OCH_3 and p-$N(CH_3)_2$ groups, which have a deeper color in the dinitrophenylbutyric than in the dinitrophenylacetic acid series.

These regularities of color variation, established by visual observations, are confirmed by reflection spectra for the substances in the solid state (in the form of very fine powders). As can be seen from Fig. 1, when the compounds contain the electron-donor OH or $N(CH_3)_2$ groups in the meta position, the reflection curves of the dinitrohydrocinnamic acid derivatives (Curves 2 and 5) are the most bathochromic, and those of the dinitrophenylbutyric acid derivatives (Curves 3 and 6) are the most hypsochromic, which corresponds to the deeper color of the former and the less deep color of the latter (Table 2). For compounds containing the same electron-donor groups in the para position, the dinitrohydrocinnamic acid derivatives take the most hypsochromic position, corresponding to their least deep color (Fig. 2, Curves 2 and 5); the relative positions of all the curves exactly correspond to the changes of color observed visually. Thus, the reflection curves shown in Figs. 1 and 2, confirm the existence of a color change sequence observed in the transition from one series of derivatives to another both in compounds containing an OH group and in compounds with $N(CH_3)_2$ group. The reflection curves for compounds with OCH_3 groups (Figs. 3 and 4) show that this sequence is lacking in these compounds. The following peculiarity should be noted here: if a OCH_3 group is present in the meta position, the curve for the dinitrophenylbutyric acid derivative is bathochromically displaced relative to the curve for the corresponding dinitrohydrocinnamic acid derivative (Fig. 3, Curves 3 and 2), although visually both compounds are characterized as pale yellow.

We consider that the principal cause of the color of these compounds in the solid state, as of the corresponding mononitro derivatives, is direct interaction between the electronophilic (BK) and the electron-donor (AK) systems by means of exomolecular forces. In the present instance such interaction is all the more probable because an electronophilic system with two nitro groups as a rule has considerable complex-forming power.

In an examination of color effects in mononitro derivatives [1,5], we attempted to explain the deeper color

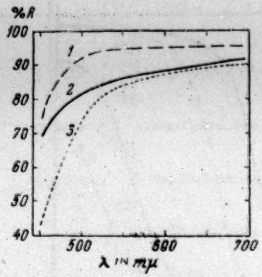


Fig. 3. Light reflection curves.
1) DPA-$NHC_6H_4OCH_3$-m, 2) DHC-$NHC_6H_4OCH_3$-m, 3) DPB-$NHC_6H_4OCH_3$-m. (The designations DPA, DHC, and DPB are the same as in Fig. 1)

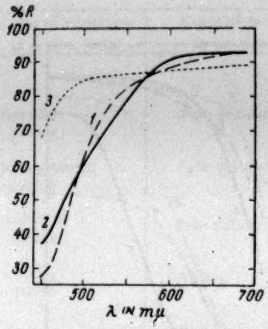


Fig. 4. Light reflection curves.
1) DPA-$NHC_6H_4OCH_3$-p, 2) DHC-C_6H_4-$NHC_6H_4OCH_3$-p, 3) DPB-$NHC_6H_4OCH_3$-p. (The designations DPA, DHC, and DPB are the same as in Fig. 1).

of nitrohydrocinnamic acid derivatives in comparison with the color of the corresponding derivatives of the other two series by the fact that the electronophilic chromophore system in p-nitrohydrocinnamic acid is rather stronger than in p-nitrophenylacetic and p-nitrophenylbutyric acids. The cause of this may be sought in the fact that in p-nitrohydrocinnamic acid the electronophilic CO group is in an even position relative to NO_2, and so produces the possibility of contrapolarizing effects which are more favorable for color than coinciding polarizing effects, which may occur (with the aid of the alternation mechanism) in p-nitrophenylacetic and p-nitrophenylbutyric acids.

The situation is made more complex by the introduction of a second nitro group in the ortho position relative to the carbon chain; as we saw, dinitro derivatives also show alternation of color change in the transition from one series of compounds to another; however, this is not always so – there is no such alternation in compounds with OCH_3 groups – and, which is most important, the sequence of color change in this instance depends not only on the electronophilic group, but also on the position of the electron-donor group (A). The cause for this, as has already been stated earlier [4] is apparently to be sought in the specific properties of the o-nitro group, which may exert a powerful direct polarizing effect. A more detailed examination and solution of this problem, however, demands additional data.

EXPERIMENTAL

γ-(2,4-Dinitrophenyl)butyric acid. In the preparation of this acid, nitric acid containing some sulfuric acid was used (85 % HNO_3, 9% H_2SO_4, 6% H_2O). 8.2 g (0.05 mole) of phenylbutyric acid* was dissolved in 55 g of this nitric acid, and 28 g of sulfuric acid (d 1.84) was added to this solution. The mixture was heated on a gently boiling water bath for 2 hours. At the end of the heating the reaction mass was poured onto ice, and the precipitate which formed was separated off and washed several times with water. After 3-recrystallizations (1 from dilute acetic acid and 2 from water) prismatic crystals were obtained, m.p. 97.5°, easily soluble in alcohol, ether, benzene, acetic acid, and acetone, in the latter even in the cold. The substance dissolves with much more difficulty in water and carbon tetrachloride.

Found %: N 11.33. $C_{10}H_{10}O_6N_2$. Calculated %: N 11.03.

* γ-Phenylbutyric acid was prepared from β-phenylethyl bromide with the aid of malonic ester as described by Fischer and Schmitz [6].

The acid chloride of γ-(2,4-dinitrophenyl)butyric acid was prepared by the action of the equivalent amount of phosphorus pentachloride on the acid. After removal of phosphorus oxychloride (under vacuum) the residual acid chloride was dissolved in a small amount of dry benzene, and the benzene solution was used for the preparation of the corresponding arylamides, a small excess (10% over the theoretical amount) of the acid chloride being used. The condensation with amines was carried out in aqueous benzene in the presence of sodium bicarbonate, similarly to the preparation of the previously described p- and m-nitrobenzoic acid arylamides [2a].

3-[γ-(2,4-Dinitrophenyl)butyramino]-anisole (Table 1, No 1). The reaction product did not separate out as a precipitate. The benzene solution was separated and the benzene distilled. The remaining liquid mass was crystallized from alcohol. This yielded a greenish-yellow substance which was recrystallized 2 more times from alcohol. It forms prismatic crystals which readily gather into hemispherical clusters, m.p. 86.5°. Crystallization from a mixture of benzene and petroleum ether yielded a lighter (almost colorless) form, m.p. 87-88°, which also crystallized in prisms. The pale form can also be obtained from alcohol by rapid cooling of an alcohol solution (sometimes the pale form also separates from solution in alcohol on slow cooling). The yellow form may be obtained pure also by recrystallization from carbon tetrachloride. Both forms are easily soluble in acetone, chloroform, benzene, and acetic acid even in the cold, are soluble fairly easily in alcohol, with greater difficulty in carbon tetrachloride, and with difficulty in petroleum ether and in ether.

Found %: N 11.98, 11.87. $C_{17}H_{17}O_6N_3$. Calculated %: N 11.70.

4-[γ-(2,4-Dinitrophenyl)butyramino]-anisole (Table 1, No 2). The reaction product was recrystallized 3 times from alcohol. This yielded a pale greenish-yellow substance which crystallized in the form of long thin plates pointed at the ends, m.p. 110.5°. It is readily soluble in acetone (even in the cold), alcohol, and acetic acid, fairly easily in benzene, and with difficulty in ether.

Found %: N 11.65. $C_{17}H_{17}O_6N_3$. Calculated %: N 11.70.

3-[γ-(2,4-Dinitrophenyl)butyramino]phenol (Table 1, No 3). The precipitate was recrystallized 3 times from alcohol. The product forms greenish-yellow crystals, m.p. 177°, easily soluble in acetone, fairly easily in alcohol and acetic acid, with difficulty in benzene, chloroform, and ether.

Found %: N 12.39. $C_{16}H_{15}O_6N_3$. Calculated %: N 12.18.

4-[γ-(2,4-Dinitrophenyl)butyramino]phenol (Table 1, No 4). The precipitate was recrystallized 3 times from alcohol. The substance forms small platelets gathered into clusters, orange-yellow in color, m.p. 163-164°, easily soluble in acetone even in the cold, alcohol, and acetic acid, with difficulty in benzene and chloroform, with even greater difficulty in ether.

Found %: N 12.44. $C_{16}H_{15}O_6N_3$. Calculated %: N 12.18.

3-[γ-(2,4-Dinitrophenyl)butyramino]dimethylaniline (Table 1, No 5). The precipitate was recrystallized twice from toluene and once from alcohol. The substance forms wedge-shaped crystals, orange-red in color, m.p. 132.5°, easily soluble in acetone, acetic acid, and chloroform, fairly easily in alcohol, benzene, and toluene, with difficulty in ether.

Found %: N 15.12. $C_{18}H_{20}O_5N_4$. Calculated %: N 15.05.

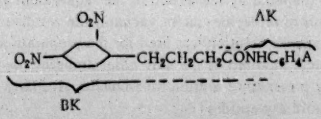
4-[γ-(2,4-Dinitrophenyl)butyramino]dimethylaniline (Table 1, No 6). The precipitate was recrystallized from toluene and [illegible] from alcohol. The substance forms rhombic crystals of a very deep red, almost black color, m.p. 126°. It is readily soluble in acetone (even in the cold), fairly easily in alcohol, acetic acid, benzene, and toluene, and with difficulty in ether.

Found %: N 15.31. $C_{18}H_{20}O_5N_4$. Calculated %: N 15.05.

Spectrum measurements. The reflection spectra were measured with the aid of an apparatus constructed by E. V. Shpolsky [7]. Details of the measurements were described earlier [8].

SUMMARY

1. A series of γ-(2,4-dinitrophenyl)butyric acid arylamides with the general formula



where A is one of the electron-donor groups $-OCH_3$, OH, $N(CH_3)_2$, situated in the meta or para position relative to the NH group, has been synthesized.

2. All the compounds synthesized proved to be colored, despite the presence of three CH_2 groups in the connecting link, which excludes the formation of a continuous conjugated chain; the color of the most deeply colored compound (with a p-$N(CH_3)_2$ group) is very deep red, almost black.

3. When the donor group is in the meta position, these compounds, like the 2,4-dinitrophenylacetic acid derivatives, have a rather less deep color than the 2,4-dinitrohydrocinnamic acid derivatives. Thus, an alternation of color change is found in the transition from 2,4-dinitrophenylacetic to 2,4-dinitrohydrocinnamic and then to 2,4-dinitrophenylbutyric acid derivatives; the color first deepens, then increases.

4. If the compound contains an electron-donor group in the para position, the 2,4-dinitrophenylbutyric acid derivatives are as a rule more deeply colored than the corresponding dinitrohydrocinnamic acid derivatives. There is an alternation of color change in the transition from one series of compounds to another, but in the reverse order, namely: there is first an increase of color (in the transition from dinitrophenylacetic to dinitrohydrocinnamic acid derivatives) followed by deepening (in the transition from dinitrohydrocinnamic to dinitrophenylbutyric acid derivatives). In both cases this sequence rule is not obeyed by compounds containing an OCH_3 group.

5. These laws of color variation, established on the basis of visual observations, were confirmed by reflection spectra obtained for the substances in the solid state.

6. The main cause of the color of these compounds in the solid state must be sought in the possibility of direct interaction between the electronophilic (BK) and the electron-donor (AK) systems by means of exomolecular forces, or the same forces which cause complex formation between nitro compounds and aromatic amines and phenols.

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PRODUCTS OF THE REACTION BETWEEN ISONICOTINEHYDRAZIDE AND FURFURAL

R. P. Veltman

According to the literature [1,2], the isonicotinehydrazone of furfural has high antitubercular activity.

A short time before these papers appeared, we prepared furfural isonicotinehydrazone. In in vitro tests and tests on experimental tuberculosis it proved more effective than phthivazide. However, the high toxicity of furfural isonicotinehydrazone in comparison with phthivazide makes its use for tuberculosis treatment impossible.

Fox [1] described the synthesis and properties of 1-isonicotinyl-2-furfurylidenehydrazine. The synthesis was carried out in methyl alcohol without the use of catalysts. The product consists of colorless needles, m.p. 217-218°. We carried out this reaction under the catalytic action of hydrochloric or sulfuric acid, and prepared a bright yellow product, m.p. 215-216°. By a study of the reaction between isonicotinehydrazide and furfural we established that the course of the reaction in a neutral medium differs from that in the presence of acids. If the reagents are heated together in water or alcohol, a colorless substance with m.p. 218-219° (I) is obtained. If an alcoholic solution of the reagents is heated in the presence of concentrated sulfuric acid, a bright yellow substance with m.p. 215-216° (II) is formed in quantitative yield. A mixture sample of the two substances shows a considerable melting point depression (188-190°).

In the presence of hydrochloric acid a mixture of the two substances, with m.p. 193-196°, is formed. The separation of pure (II) from this mixture requires repeated washing with alcohol and crystallization from glacial acetic acid. If the colorless substance (I) is warmed with sulfuric or hydrochloric acid in alcohol solution, it is converted into yellow (II).

Both substances inhibit the growth of tuberculosis bacilli in exceedingly low concentrations of the order of 1: 20,000,000.

Elementary analysis data for both substances correspond to the formula for furfural isonicotinehydrazone, $C_{11}H_9O_2N_3$.

We believe that the two substances are different modifications of furfural isonicotinehydrazone, on grounds of the common method for their preparation, the easy conversion of one into the other, and their equally high antitubercular activity.

EXPERIMENTAL

Isonicotinehydrazide, m.p. 172°, and freshly distilled furfural (b.p. 162°) were used for the reaction. Two series of experiments were carried out: in one, 0.2-0.3 ml of concentrated acid was added, and in the other no acid was added.

1 g of isonicotinehydrazide and 1 ml of furfural (45% excess) in 10 ml of solvent were heated under reflux for 1 hour. The precipitated crystals were filtered off on cooling. The colorless product was crystallized from alcohol, and the yellow product was washed several times with warm alcohol and crystallized from glacial acetic acid. The results of the experiments are shown in the table.

TABLE

Solvent	Acid	Color of product	Melting point	Yield (%)
Water	–	Colorless	218–219°	89
Alcohol	–	Colorless	217–218	83
Alcohol	Hydrochloric	Yellow	193–196*	90
Alcohol	Sulfuric	Yellow	215–216	97

* After repeated crystallization, m.p. 215°.

Properties of the substances formed. (I) consists of colorless long needles, m.p. 217-218° (from alcohol). It is soluble with difficulty in water, dissolves easily in hot alcohol but the solubility is low in cold. When a solution in alcohol is warmed with a drop of sulfuric acid, it turns yellow. When the solution is boiled with alcohol and sulfuric acid, a yellow precipitate is formed which begins to melt at 193°.

Found %: N 19.32, 19.53. $C_{11}H_9O_2N_3$. Calculated %: N 19.53.

(II) forms coarse yellow plates, m.p. 215° (from glacial acetic acid); m.p. 180-186° (from water). It is soluble on warming, but not in the cold, in water and in glacial acetic acid. It is soluble with difficulty in hot alcohol.

Found %: N 19.38; 19.53. $C_{11}H_9O_2N_3$. Calculated %: N 19.53.

SUMMARY

1. Two modiciations of the hydrazone are formed in the reaction between isonicotinehydrazide and furfural: colorless (m.p. 218 - 219°) in a neutral medium, and yellow (m.p. 215-216°) in an acid medium.

2. The white hydrazone is converted into the yellow modification when it is heated in alcohol with mineral acid. When the yellow hydrazone is heated with water, it is partially converted into the colorless product.

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INVESTIGATION OF ACONITIC ALKALOIDS

VI. CONVERSION OF METHYLLYCACONITINE INTO DELSEMINE

A. D. Kuzovkov

Delsemine was discovered and studied by S. Yu. Yunusov and N. K. Abubakirov [1]. Interest in this alkaloid increased after P. M. Dozortseva and M. D. Mashkovsky [2] showed that it has curare-like properties.

The present paper deals with the possibility of the conversion of methyllycaconitine, the commonest alkaloid of the Delphinium genus of plants, into delsemine.

We studied the reaction between methyllycaconitine and ammonia in aqueous alcohol, ether, and chloroform solutions. Delsemine was formed in all cases, the highest yield (68%) being obtained in ether solution. When an ether solution of methyllycaconitine was left to stand with a small amount of aqueous (12%) ammonia, the delsemine formed, because of its low solubility in ether, was precipitated in the form of beautiful large crystals; the precipitation was complete in 4 days. The conversion of methyllycaconitine into delsemine takes place in conditions close to those used in the extraction of alkaloids from plants, moistened with aqueous ammonia, by means of dichloroethane; a solution of methyllycaconitine in 10% acetic acid was made alkaline to phenolphthalein with 12% aqueous ammonia, shaken with an equal volume of chloroform, and left for twenty-four hours, when delsemine was isolated in 25% yield, and 30% of unchanged methyllycaconitine was obtained.

Our observations lead to the view that delsemine is formed from methyllycaconitine • during the extraction of the raw material moistened with ammonia, which casts doubt on the presence of delsemine as such in the plant. This doubt is also supported by the fact that the literature contains no reference to the possibility of isolating delsemine from plants by any method without treatment of the plant by ammonia, such as alcohol extraction, and also the fact that methyllycaconitine was found simultaneously with delsemine in Delphinium semibarbatum and Delphinium oreophilum. In our opinion, experiments necessary to determine the origin of delsemine will be carried out by workers who have a raw material from which delsemine was extracted at their disposal.

EXPERIMENTAL

Methyllycaconitine perchlorate recrystallized twice from 70% alcohol was used.

M.p. 193-195°, $[\alpha]_D$ + 25.8° (c 1, C_2H_5OH).
Found %: C 54.76; H 6.81; N 5.39. $C_{37}H_{50}O_{10}N_2 \cdot HClO_4 \cdot 1.5H_2O$. Calculated %: C 54.84; H 6.67; N 3.46.

These constants and composition agree with those for methyllycaconitine perchlorate; m.p. 194-195° [1], $[\alpha]_D$ + 25.4°.

Conversion in ether solution. 1 g of methyllycaconitine perchlorate was triturated with 10 ml of 12% aqueous ammonia. The base was extracted with ether. 3 ml of 12% aqueous ammonia was added to the combined ether extracts, 50 ml, and the solution was shaken and left to stand. The first silky crystals appeared after 24 hours, and after 48 hours the precipitate contained numerous large crystals. After 96 hours the alkaloids were extracted with 10% H_2SO_4. The acid extract was made alkaline with 12% aqueous ammonia in the presence of 20 ml of ether with vigorous shaking, and a crystalline precipitate of delsemine was formed immediately; this was washed with water and ether after filtration. After drying at 80° the yield was 0.6 g (68%); the substance softens at 122-124°, melts with frothing at 127°, and the metal becomes clear at about 130°. No melting point depression was found in a mixed sample with delsemine.

• The alkaloid avadkharidine isolated earlier by us from Aconitum orientale is apparently formed similarly from lycaconitine.

0.0650 g sub., 3.0 ml alcohol, l 1 dm, α + 0.45, $[\alpha]_D$ +41.6°.

After crystallization from 50% alcohol the melting point and the specific rotation were not measured.

Found %: C 63.50; H 7.57; N 5.80. $C_{37}H_{53}O_{10}N_3 \cdot 0.5H_2O$. Calculated %: C 62.69; H 7.62; N 5.92.

Conversion in chloroform solution. The base obtained from 1 g of methyllycaconitine perchlorate was dissolved in 50 ml of 10% acetic acid. 12% aqueous ammonia solution was added till the solution was strongly alkaline to phenolphthalein, followed by 100 ml of chloroform, the solution was shaken vigorously and left for 24 hours. The chloroform layer was extracted 3 times with 10% H_2SO_4. The combined acid extracts (40 ml) were made alkaline by means of 25% aqueous ammonia in presence of 20 ml of ether with vigorous shaking and cooling. The precipitated delsemine was washed with water and ether on the filter. The yield was 0.2 g (25%); the substance softens at 122°, melts with frothing at 125°, the melt becomes clear at about 128°, $[\alpha]_D$ +41.4°. The mother liquor after isolation of the delsemine was acidified with 20 % H_2SO_4, and a solution of magnesium perchlorate was added. Upon standing 0.3 g of methyllycaconitine perchlorate, m.p. 189-190°, was precipitated.

Conversion in alcohol solution. The base prepared from 1 g of methyllycaconitine perchlorate was dissolved in 10 ml of alcohol, 2 ml of 25% aqueous ammonia was added, and the solution left for 96 hours. The alcohol was evaporated off under vacuum. The residue was dissolved in 30 ml of 10% H_2SO_4. When the solution was made alkaline in the presence of 20 ml of ether, 0.4 g of delsemine (yield 45%) was precipitated after cooling and vigorous shaking.

SUMMARY

1. It was established that methyllycaconitine is converted into delsemine by the action of ammonia in various solvents.

2. The view is put forward that delsemine is not contained in the plant as such, but is formed from methyllycaconitine during extraction of the raw material moistened with ammonia.

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DISCUSSION

THE RELATIONSHIP BETWEEN THE HEATS OF FORMATION OF CHEMICAL COMPOUNDS AND THE POSITION OF THE ELEMENTS IN D. I. MENDELEEV'S SYSTEM*

A. F. Kapustinsky

These comments refer to the paper which touches upon the problem of the relationship between the Mendeleev system (inaptly termed "table" by V. P. Shishokin, which tends to minimize somewhat the significance of D. I. Mendeleev's work) and thermochemistry. As is known, the approach to the problem was, in the first approximation, formulated by the thermochemical logarithmic curve rule [1], which indicated the relationship between the basic concepts of thermochemistry – the heats of formation – and the fundamental characteristics in Mendeleev's system – – the groups, periods, and positions of the elements.

Despite the fact that this generalization has found fruitful applications in practice and in theoretical analysis, which have been published (although, to judge from V. P. Shishokin's paper, unknown to him), V. P. Shishokin considers the rule to be both theoretically unfounded and unconfirmed. His reason for the first is the use of Hume-Rothery's views, which do not reflect the stepwise variation of the atomic radii in the groups, in the derivation of the rule. Leaving aside the disagreement between V. P. Shishokin and Hume-Rothery, we must point out that his comment would have significance if the logarithmic curve rule was the direct and unique consequence of these views, which is not in fact the case. If he had taken the trouble to become more closely acquainted with the original, he would have found (pp 569-570) that the impossibility of a strict deduction was stressed, and that the present author [1] used Hume-Rothery's views in order to show clearly the logical connection between the values in question; this qualitative and "illustrative" approach renders the degree of accuracy of Hume-Rothery's constructions unimportant. The second defect is attributed to the allegedly observed inconsistency between the rule and the facts, namely, the appearance not of a regular but of a secondary periodicity in the groups. In proof, Fig. 1 is given, which shows the relationship between the heats of formation of alkali metal chlorides and the logarithm of the atomic number, drawn to two scales – that used in the paper by A. F. Kapustinsky [1], and an enlarged scale. Having received a zig-zag instead of a straight line, V. P. Shishokin asserts that the logarithmic curve rule is "unconfirmed".

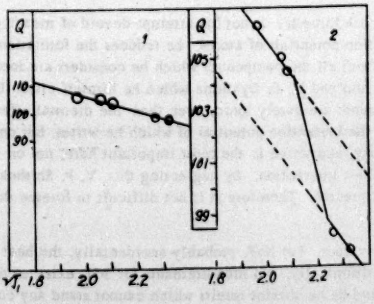

Fig. 1. Relationship between the heat of formation of alkali metal halides Q and the square root of the first ionization potential I. 1) Scale 1 cm = 10 kcal., 2) scale 1 cm = 1 kcal.

The gross error committed here by V. P. Shishokin is a failure to understand the necessity for at least an approximate agreement between the accuracy of the graph and the accuracy of the values plotted on it. Having arbitrarily and unjustifiably increased the ordinate scale 10 times (!) he left the dimensions of the points on the graph unchanged, and so obtained considerable scattering of the points. He would have generally obtained similarly farcical results (in relation to the laws of physical chemistry) by an arbitrary increase of the scale by tens or hundreds of times in a graphical representation of any experimental results. A curious illustration is provided by his own evaluation, shown in Figure 2, and represented on the left-hand side of the figure in the present paper on the scale chosen by V. P. Shishokin. By increasing

* Comments on the paper by V. P. Shishokin, published in J. Gen. Chem., 24, 745 (1954) (C.B. Translation p.753).

the scale 10 times, as was done by him, we obtain, instead of the single straight line (1) described by him, two different straight lines (2); this example relates to well-known substances (chlorides), and the graphs are based on the same source [2] as was used by him. Thus, had he applied his own method to himself, V. P. Shishokin would have easily been able to refute his own assertions.

The reader will treat V. P. Shishokin's reasoning on its merits. However, this is not the end of the matter. Ignoring the existing literature, V. P. Shishokin intends to "refute" the thermochemical logarithmic graph rule as being allegedly contrary to Biron's secondary periodicity which he also asserts (pp 745-746) to be unknown to A. F. Kapustinsky. The latter, however, cannot be included among those about whom V. P. Shishokin writes: "Biron's work remained unnoticed both by Russian and by foreign workers". As early as 1951, or before the appearance of all the papers cited by V. P. Shishokin in this context, I publised in Proc. Acad. Sci. USSR an attempt at a theoretical treatment of Biron's secondary periodicity; this was followed by publications by S. A. Shchukarev and his co-workers, which made possible a new approach to the treatment of this important phenomenon and of its manifestations in thermal effects. But does this law, the discovery of which is Biron's great achievement, introduce chaos into science, or lead to the rebuttal of known facts ? Neither Biron nor any worker who soberly assessed the facts made any such blatant assertion. Secondary periodicity only extends and amplifies Mendeleev's law and in no way refutes or obscures it. In the same way, the thermochemical logarithmic graph rule solves the problem in the first approximation with the aid of the classical and fundamental atomic characteristics of the elements in Mendeleev's system. Secondary effects and finer shades of thermal effects are then considered on the basis of secondary periodicity, which provides a second approximation to reality.

V. P. Shishokin in his paper ignores the development of the problem as a whole and also fails to analyze the limits of applicability of the rule, neglects explanations of causes of deviations, and discussions of more precise formulations; to judge from the paper, V. P. Shishokin is unaware of the work of O. Ya. Samoilov, K. B. Yatsimirsky, S. I. Drakin, B. M. Yakushevsky, M. S. Stakhanova, and other Soviet and foreign workers, devoted to favorable development of the rule. Nevertheless, we venture to suggest that it is desirable for every critic to be acquainted with the subject which he proposes to attack.

While in the first part of his paper V. P. Shishokin attempted to belittle the thermochemical logarithmic graph rule, in the second part he attempted to find a relationship between ionization potentials and heats of formation and, it must be said at once, with equal lack of success.

To the extent to which it is reasonable to consider thermal effects in relation both to ionization and to the position of an element in Mendeleev's system, this question had already been studied by K. B. Yatsimirsky [3], when the logarithmic rule, so disliked by V. P. Shishokin, was again used. In general, between what values is it permissible to seek an expression for their relationship? Between values which are in a logically rational dependence on each other. For example, the work of ionization is clearly related to the particle radius, hence the basis for K. B. Yatsimirsky's work and therefore its success.

Nevertheless, V. P. Shishokin apparently does not even ask himself: is not his attempt devoid of meaning ? In trying to relate heats of formation of compounds to ionization potentials of atoms, he reduces the formation of chemical compounds to a purely ionic process, although far from all the compounds which he considers are ionic, which he could have found, even from the book by Ya. K. Syrkin and M. E. Dyatkina which he himself cites. But this is not all. Even if it is imagined that all existing compounds are purely ionic, even then the thermal effect, as can be seen from the Born-Haber cycle, depends not only on the ionization potential of which he writes, but on the heats of change of state of aggregation, on the electron affinity, and, which is the most important here, not on values which apply to individual isolated ions but on the energy of their interaction. By neglecting this, V. P. Shishokin destroys the physical meaning of an examination of a chemical process. Therefore it is not difficult to foresee the results of such an undertaking.

He extrapolated and interpolated a total of six thermal values. For NaF, probably accidentally, the heat of formation practically coincided with the value obtained logarithmically. No measurements for SCl_4 exist, so that a comparison cannot be made. For fluorides of Sr, Mg, Ca, and Be he obtains results which cannot stand any comparison with direct thermochemical measurements, which V. P. Shishokin asserts to be inferior to his own calculations – a rash assertion without any confirmation. Thus, all six results lead to nothing.

We will incidentally point out that V. P. Shishokin used obsolete data from Kaye and Laby [2], which no one working in thermochemistry does, since there are available special critical collections of thermochemical constants published in the last 5 years. What, then, is the final result of this blind empiricism, loudly claimed as "laws" by the

author? Complete chaos. For the heats of formation of the alkali halides he finds a linear relationship with the square root of the ionization potential; for the halides of Al, Pb, and Sb, with the first potential for the halogen; for compounds of Al and Group 6, with the logarithm of the sum of the first two potentials of these elements; for the 3rd period, with the square root of the quotient obtained by division of the group potential by the group number, etc. A careful examination of this picturesque mixture of "laws", sometimes justified, and sometimes not, discloses an even greater diversity than is represented by the author himself.

The scope of this note does not permit a further extension of the discussion of the errors and misconceptions which fill V. P. Shishokin's paper. However, even the above is sufficient to show that it can in no way serve the development of general, physical, and inorganic chemistry.

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